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SOME HISTORICAL REMINDERS IN HOSPITALIZATION

THOS. J. HELDT, M.D.*

In the history of medicine, historians are still searching antiquity for the origin of the basic idea resident in hospitalization. In prehistoric times, the biological process of mating probably carried with it consideration of the handicaps and the ills of mates and offspring. Historic time is being extended and expanded as fossils, tablets of clay, writings on papyrus, and hieroglyphic markings in caves are eagerly sought out, preserved, and translated.

Ancient China practiced medicine of a sort some thousands of years before the Christian era. The Chinese were medically guided by the aphorisms of their legendary emperor, Huang-Ti (2698-2598 B. C.) alone for 4,000 years. The materia medica of that medical system was as extensive as it was inaccurate; its anatomy and its physiology were fantastic; and, great efficacy was ascribed to acupuncture and to the moxa. The Huang-Ti system of medicine was followed by the Chinese until well into the 14th century A. D., since which time there has been a gradual infiltration of other medical ideas. The leaven of Kung-fu-tse (Confucius, 551-478, B. C.) was added in the 4th century B. C.

Some historians think the Egyptians and the Assyro-Babylonians were the oldest purveyors of medicine. Their papyri and steles disclose an extensive materia with an associated chemistry and pharmacy. The priests of their time had specialists who attended separately to eyes, ears, teeth, and other parts of the body, but, beyond the limited cutting apart of tissues common to embalming, dissection was a sacrilege. On a stele of Nineveh dating from between 1,000 to 2,000 B. C. is recorded what is judged to be the oldest illustration of infantile paralysis. The Ebers Papyrus was written about 1552 B. C.

Ancient India, too, is rich in medical lore. Its Vedic literature, conservatively estimated as having been collected and composed about 4,000 B. C., contains much of medical interest[1]. Certain of the books of the Susruta Samhitas are especially valuable inasmuch as they record some of the attainments of Susruta I (Ca. 600 B. C.), the father of Hindu surgery[1]. Susruta II is credited with having discovered cataract-couching unknown in his time to the surgeons of ancient Greece and Egypt[1]. The Oath of the Hindu Physician, not very dissimilar from the Hippocratic oath, was in effect and adequately recorded before the birth of Hippocrates.

The Greeks have been accredited the real founders of medicine and the prominence of Hippocrates (460-377 B. C.) and his works are such that the credit seems well founded. The father of Hippocrates was a priest of the Aesculapian Temple of Cos, which temple was only one of some 80 similar temples of ancient Greece. Although Walsh[2] seems unwilling to concede that hospitals worthy of the name existed prior to the birth of Christ, it may be judged that these Hellenic temples and the hospitals of a kind in old India and in ancient Ireland[3] should be looked upon as the prototypes of our present day hospitals.

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The designation *hospital* is difficult of precise definition, but prominent in its meaning is the Roman *hospes* denoting a guest (W. Aryan, ghostis). The etymology of the words *hospice* and *hospitium* is likewise dominant in implying welfare and asylum. That the patient be respected as the guest of his physician and a hospital be regarded as a guest-house is probably part of a basic concept. Such a concept has been beset by many variables throughout the centuries and still is to this very day.

In the third century B. C. edicts of Asoka, the great Buddist emperor of Hindustan, were carved on rocks and pillars throughout his kingdom[4]. Wise[5] states (p. 390) that some of these edicts, "relate to the establishment of a system of medical administration throughout the dominions of the supreme depots of medicine for the sick of man and animals." Wise holds that these are the first hospitals on record. Withington[6] records that in the Maharansa, or Cingalese chronicle, it is related that when King Duttha Gamane was on his deathbed in 161 B. C. he ordered the record of his deeds to be read to him. It included: "I have daily maintained at eighteen different places hospitals providing suitable diet and medicines prepared by medical practitioners for the infirm."

The origin of the prechristian Greek hospitals is inextricably inter-woven with the Aesculapian temples of healing, the most notable of which was that at Epidaurus.

Among the hospitals of the early Christian era the following must be mentioned: The hospital built at Byzantium by Emperor Constantine in 330 A. D.; The Hospital of St. John of Jerusalem built by Emperor Justinian in 350 A. D.; and the hospital founded by Caliph Welid for the Arabs in 707; but the most famous of the Moslem hospitals were those of Damascus and Cairo, especially the Mansuri Hospital of Cairo. We are told[3] that Ahmed ben Toulon, first independent ruler of Egypt, founded a hospital there in 874 at a cost of about £30,000. That hospital included "a department for insane patients." As a type of the mediaeval hospital, the Hôtel Dieu of Paris stands out[8]. It is said to have been founded in 660 by St. Landry, then Bishop of Paris. It was enlarged by St. Louis in the 13th century.

In England[3] "the earliest record of a hospital is connected with the name of Archbishop Lanfranc, who about 1070 built wooden tenements outside the west gate of Canterbury for the reception of persons suffering from the king's evil. The Priory and Hospital of St. Bartholomew's were founded by Prior Rahere in 1102. St. Thomas' Hospital by the Prior of Bermondsey in 1213, and the Prior and Hospital of Bedlam in 1247."

It is declared that hospitals were present in Mexico long before the discoveries of Christopher Columbus. The first hospital in the Western Hemisphere of clearly known origin was that built by Commander Ovando in Santo Domingo, 1501-1508[7]. He named it San Nicolàs after his own patron saint. Cortés had barely wrested Mexico City from the Aztecs, when probably about 1523, or even before, he laid the cornerstone of the Hospital de la Purisima Concepcion at Huitzilan. Cortés left funds in his will for its completion and support, and his ashes are buried there. The name of the hospital was later changed to Hospital del Marqués, and still later to Jesus Nazareno, under which designation "it still continues its useful life, the oldest of all hospitals at present on American soil."[7]

The first asylum for the insane in America was San Hipolito in Mexico City, organized in 1566 or 1570 by Bernardino Alvarez, "who after devoting ten years of his life to caring for patients at La Concepcion (the oldest existing hospital in America) had seen the need of such an institution. The first asylum for insane women was organized by Sayago, a carpenter, in 1700."[7]

In Canada, the founding of Quebec by Samuel De Champlain (1567-1635) in 1608 soon awakened need for hospital care for the sick of whatever type. Through his surgeon, Bonnerme (died 1609), his friend, Louis Hébert, and a second surgeon, Adrien Duchesne (to Quebec in 1618) Champlain strengthened his medical needs. When Quebec was restored to the French by the Treaty of St. Germaine-en-Laye (March 29, 1632), the foundation of the Hôtel Dieu was planned. It was one of the chief objects of Father le Jeune duly set forth in his writings "The Relations of the Jesuits." These Madame de Comballet, Duchess d'Aiguillon, niece of Cardinal Richelieu, read, and was so impressed that she began correspondence on the subject with Father le Jeune in 1636. Funds were subscribed, a twelve acre grant of land obtained, and temporary quarters provided. Thus, Hôtel Dieu of Quebec came into being[9] under the full name, Hôtel Dieu du Preciéux Sang, in 1639.[10]

Hôtel Dieu de St. Joseph in Montreal was established in 1644.[10] In the history of its founding, the organizing efforts and the nursing care given by Jeanne Mance (1606-1673) are so outstanding that it should not be amiss to style her the Florence Nightingale of Canada.

The first hospital building distinctly for the mentally ill of Canada was a small dwelling erected by Monseigneur de Saint Vallier (John Baptiste Vallier, 1653-1727), second Bishop of Quebec, near Hôtel Dieu in 1714. This small building was given over largely to the care of insane women. Hence, very shortly, under the superintendency of the Bishop, a similar dwelling was erected nearby to accommodate 12 insane men patients.

The time and the place of the first hospital of recent times to be located within the present area of the United States is differently given by various writers. Moll* gives Manhattan Island in 1663.[7] MacQuiddy[11] states: "The beginning of the hospital system in the United States proper is very difficult to follow. Some would have us believe that in 1663† there was a small hospital established on Manhattan Island to care for the sick soldiers and negroes in the East India Company. The history, however, is meagre, and we do not know what became of this institution." Ransom[12] says: "The first hospital to be established in the territory which later became the United States of America was in what is now New York City. In 1658, at the suggestion of Master Jacob Hendricksen Varrevanger, Surgeon to the Dutch West India Company, a hospital was erected for the care of sick soldiers, who previous to that date had been billeted on private families. It also served the Negro slaves of the Dutch West India Company. New York City, then called New Amsterdam, had

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*In correspondence with the librarian of the Henry Ford Hospital, Moll states: "The name before the word 'Island' in the statement about hospitals in my Aesculapius, p. 139, should read, of course, 'Manhattan,' not 'Long'."

†MacQuiddy gives as his reference: Hospitals and Their Origin and Evolution. John Foote, M.D., Washington, D. C. Popular Science Monthly, May 1913 Vol. 82:478-491.

a population of about 1000, of whom a considerable number were negro slaves. In 1680 this hospital building, then known as the 'Old Hospital' or 'Five Houses,' was sold and a new and more modern building erected in its place."

Foote[3] states (p. 489): "Early in the eighteenth century pest-houses for contagious diseases were established in various towns on the Atlantic coast. A permanent hospital for these ailments was built in Boston in 1717."

Records of a monthly meeting held August 25, 1709, by the Society of Friends of Philadelphia, state[13]:

> "Thomas Griffith is ordered to pay Edward Shippen to the value of Eight Pounds Sterling when there is stock in his hands, towards defraying the charges of negotiating matters in England in relation to the School Charter and one that is endeavored to be obtained for an Hospital, according to the agreement and concurrence of the Meeting some time past, and was accordingly to send over by Isaac Norris to request of Gov. Penn who was willing to grant the same; but, upon advice thought it proper to have the School and Hospital in one which this meeting desires may be moved again by James Logan, who is now going over to England."

This seems to have been the first effort toward establishing a hospital in Philadelphia, but this beginning smoldered until it received more and more the attentions of Dr. Thomas Bond (1712-1784) and Benjamin Franklin (1706-1790). Both were very influential in presenting a petition "To the Honourable House of Representatives of the Province of Pennsylvania January 23rd, 1751." After a second reading of the petition, January 29, 1751, favorable action followed. Judge John Kinsey's mansion on the south side of Market Street below Seventh was leased as a temporary hospital. On February 10, 1752, Margaret Sherlock, one of the sick poor, "was the first patient received and also the first one cured . . . the first lunatic pay-patient, a woman, was admitted March 5, 1752." Thus was permanently established the Pennsylvania Hospital with first thought to, the "insane" and "the sick poor." Morton[13] very pertinently states: "The opening of the Pennsylvania Hospital inaugurated a new epoch in the treatment of lunatics in this country, as it began by receiving them as patients suffering with mental disease, to be subjected to such treatment as their cases required, with a view of their ultimate restoration to reason, instead of simply confining them as malefactors."

Manhattan Island and its environs were early a vortex of colonial interests and problems[14]. In 1736, the City of New York completed the construction of its first "Poorhouse, Workhouse, and House of Correction." In the cellar of the west end of this building, special dungeons were built for the insane[15]. The failure of this institution to provide adequate care for the mentally ill led progressively to the founding of the New York Hospital. Its royal charter was granted in 1771, but due to a devastating fire, the Revolutionary War, and post-war conditions, its construction was delayed. It was finally opened in 1791. Its first mental patient was admitted on September 18, 1792. Within five years, cellar care of the insane was found so inadequate that a third story was added to each of the two hospital wings[15] and by 1806 it was decided to erect a separate building for the insane. On July 14, 1808, the "Lunatic Asylum" of the New York Hospital, then located on Broadway at Worth

Street, was opened for the reception of patients. "Today (1941) it would be called the psychopathic or psychiatric department of the general hospital." Lack of space for enlarging this asylum on the grounds of the New York Hospital and to provide improved facilities led to its removal in 1821 to the new Bloomingdale Asylum in the country[16]. The Pennsylvania Hospital made a similar separation in 1841[15].

Bellevue Hospital, New York City, had its origin in the "Publick Workhouse and House of Correction of the City of New York" (See above). Its original site was where the old City Hall now stands. "The site ultimately chosen (1811) was part of the old Kips Bay Farm containing slightly more than six acres. On this site there stood at that time the first building to bear the name of Belle Vue Hospital and this location is the site of the present Bellevue Hospital.[17]" Bellevue's "Insane Pavilion" was not constructed until 1879. It was planned to serve only for detention and observation. Out of this "Insane Pavilion" gradually evolved the psychopathic hospital of Bellevue[18] within "the largest general acute hospital in the world."

The first institution planned and organized solely for the care of the mentally ill in the United States was opened at Williamsburg, Virginia, in 1773. It was then given the title, "The Court of Directors of the Public Hospital for Persons of Insane and Disordered Mind[16]." It is now called, the Eastern State Hospital of Virginia.

If we were to study closely the rises and the falls in the life history of the hospitals enumerated in the foregoing pages, it would be found that appropriate care of the sick, especially the mentally ill, had been more often lost than adequately regained[19]. This is true of our own day.

Just when the designation *hospital* added onto itself the supplement — *general* — is not clearly recorded. Apparently it was a very gradual increment added to imply that certain hospitals were organized and equipped to care for all types of patients; yet, at the same time, there were notable exceptions. Any patient requiring special or prolonged care was all too soon set aside from other patients. This has been, and still is, the lot of the mentally ill patient most of all. Segregation, always segregation, is too much in the fore.

Hurd[20] in quoting from "Fifth Geo. IV* Appendix No. 1 to Report to Legislative Council, 10th February, 1842, by special committee" remarks: " The lengthy report submitted by the committee gives various interesting statistics and other details concerning the insane confined in the Hôspital Général at Quebec, the Hôspital Général at Montreal, both of which establishments were under the charge of the Grey Nuns . . ." Hamilton[15] remarks: "The first and second general hospitals in the United States, the Pennsylvania Hospital and the New York Hospital, both antedate the Revolution . . ."

"Nerve clinics" for the treatment of nervous disorders were established in Philadelphia in 1867 and in Boston in 1873. The out-patient department in the mental hospital dates from 1885 when such service was provided the Pennsylvania Hospital in Philadelphia[18].

*The expression, "Fifth Geo. IV" is just an official way of quoting documents presented to the Canadian Parliament: 1824 is the fifth year of the reign of King George IV of England.

Provisions for the hospital care of the mentally ill have varied directly with the requirements of nations, states, provinces, and communities. Indirectly, arrangements have varied with location and relationship of the hospital or parts thereof to teaching institutions, whether they have been operated as independent units, or connected with a general hospital. It is in connection with the last mentioned relationship that we desire here to make a few emphases.

The Albany Hospital was opened in 1849 in a building previously used as a jail. In 1898 these quarters were abandoned for a new institution in the suburbs of the city. The new hospital consisted of a series of buildings connected by corridors. This construction granted opportunity for the addition of a pavilion for the mental disorders. "Pavilion F." was added, and opened to patients on February 18, 1902[21].

This example of the connecting corridor was not granted the importance it merits and hospital buildings for the care of the mentally ill, often on the grounds, but separate from the parent, of general hospital buildings, became common. A few may be mentioned: The State Psychopathic Hospital at Ann Arbor, 1901-1906; The Psychopathic Hospital of the Boston State Hospital, 1912; The Henry Phipps Clinic of Johns Hopkins Hospital, 1913; Iowa State Psychopathic Hospital at Iowa City, 1920; Colorado Psychopathic Hospital at Denver, 1925; and, the Galveston State Psychopathic Hospital at Galveston, Texas, 1931. These hospitals, of course, are connected with teaching institutions. All the more might be the deisre to see in them better examples of close relationship rather than isolation.

Schooled in the thoughts of Thomas W. Salmon (1876-1927), Heldt[22] in 1923 was offered the opportunity to organize a Division of Neuropsychiatry in the Henry Ford Hospital. Heldt insisted that such Division should be an integral part of the central organization of the general hospital and a component part of the Department of General Medicine. These premises were granted and neuropsychiatric in-patients of all types, psychotic and nonpsychotic, have been accepted continuously since August 1, 1923[23]. The primary requisite for the founding of a division of neuropsychiatry in a general hospital is a full-time well qualified neuropsychiatrist who is thoroughly intent on the project and willing, night and day, to give it his undivided attention. All other things, however important and helpful, are secondary[24]. Administrative demands call for patience and adaptation, especially during active military periods[25]. An out-patient clinic was maintained from the beginning and a mental hygiene program was always in evidence[26]. A division of neuropsychiatry can be conducted successfully and profitably in any general hospital willing to give adequate time and thought to this urgent need. Isolation is avoided, no heavy locked doors or barred windows, the sexes are not separated, the seriously psychotic patients do gravitate to a first floor ward but borderline neuropsychiatric patients are admitted and treated in all parts of the hospital "mixed in" with other types of patients.

Bennett[27] states that since 1924 he has been actively engaged in establishing psychiatric divisions or wards in general hospitals, four in the hospitals of Omaha, and more recently that of the Herrick Memorial Hospital of Berkeley, California. The Psychiatric Department of the Bishop Clarkson Memorial Hospital of Omaha was established in January of 1936.[28] The opening dates of the psychiatric departments

fostered by Bennett in the other three Omaha hospitals are not available at this writing. That the administrative problem of conducting a division of neuropsychiatry within a general hospital is not an easy task must be granted by all who undertake it.[29] Bennett has mobilized his experiences well, and has graphically portrayed them in exhibits before the American Medical Association in 1950[30] and 1951[31], and the American Psychiatric Association[32].

In 1926, "when the Strong Memorial and Rochester Municipal Hospital was opened a psychiatric ward was included[33]."

In 1929, a Psychiatric Unit was opened in the Mercy Hospital, Canton, Ohio[34]. O'Brien very appropriately comments: "The treatment of mental disorders in a general hospital is not new, the question in my mind is why was it ever discontinued?"

In 1933, the Elizabeth General Hospital and Dispensary, Elizabeth New Jersey, opened its in-patient department for neuropsychiatric patients, "12 beds . . . in a separate wing." MacLeod[35], as lay superintendent, very encouragingly remarks: "We feel genuinely proud to have foreseen the demand for facilities in general hospitals for the care of the psychiatric patient by five years and to have been among the pioneers."

In 1934, the Colorado General Hospital of Denver organized its psychiatric services under the guidance of Ebaugh and Billings[36-37], and, Stanley Cobb established a psychiatric ward in the Massachusetts General Hospital[33].

In 1938, Ebaugh[38] organized a psychiatric unit in Queen's Hospital, Honolulu, with both in-patient and out-patient facilities. In the same year, Harris[39] outlined the psychiatric services of the John Sealy General Hospital in Galveston. Since 1938 there has been less hesitancy in adding psychiatric services to general hospitals, albeit too often as annexes.

Hamilton (1878-1951) stated[15]: "In 1844, . . . there were twenty-two public and corporate institutions for the mentally ill and three private institutions in the United States; one in New Brunswick, one in Ontario, and psychiatric services were attached to two general hospitals in Quebec." Ninety-five years later, in 1939, Heldt[22] listed 153 hospitals, looked upon as general hospitals, which would admit psychiatric patients. Now, in 1951, Bennett[27] reports 328 general hospitals in the United States which grant psychiatric service. Favorable progress is slowly going forward.

In considering the background of attitudes, perspectives, and trends, it is well to reread the lectures of Farrar[40] to the senior students of the Johns Hopkins Medical School in 1907. Overholser[41], in his "An Historical Sketch of Psychiatry," reminds us that Hippocrates stated that the art of medicine consists of "the physician, the patient, and the disease." Overholser closed his scholarly epitome in 1949 with these words: "The crying need today is for a synthesis of all the schools of thoughts and methods of approach; no one method has a monopoly of the truth." Russell[42] (1863-1951) very aptly records the "hospitalization of the asylums." In addressing the American Psychiatric Association in May, 1925, Pratt[43] declared: ". . . . until the psychiatrist shall become as familiar a figure on the wards of the general hospital as the surgeon and the internist, medical science cannot hope to discharge its fullest

duty to those who are commended to its care." Dribben and Barrera[44] tell us in 1951 what has happened at Mosher Memorial Pavilion since 1902. All is very much to the good.

Priorities are usually more relatively contemporary than events rigidly fixed in chronology. Furthermore, viewed in various lights and in different perspectives, they often blend inconspicuously into the natural settings of their time. Only recently, September, 1951, Adele[45], in her article: Care of the Mentally Ill in the General Hospital reported: "At the 690-bed St. Francis Hospital, the mentally ill were cared for in a specially organized department as early as 1880, when a Sister became mentally ill. . . . She was admitted to St. Francis Hospital as their first psychiatric patient . . . and in 1884, this Hospital applied for a state license." Diller[46] in March of 1905 emphasized the status of this Hospital in these words:

"St. Francis', a general hospital of Pittsburg, with its four well-equipped wards for patients who exhibit departures from normal health, has for years exemplified the ideas above advocated. I know of no similar hospital in this country. The new city hospital of Nuremberg has provided a small number of beds for "insane" patients; and in a few other general hospitals in Europe similar provision is made."

In May of 1906, Diller[47] further stressed general hospital care of the mentally ill as follows:

"Many patients with acute psychoses recover within two or three months; and how well it is if the recovery takes place in a general hospital rather than in a "lunatic asylum." It means to the patient and his friends that he has been sick rather than "insane" and that the stigmata of insanity and the lunatic asylum do not attach to him.

Chronic patients or those who become chronic should not be treated in the general hospital, nor should those who are manifestly incurable. This rule should, to my mind, apply to all patients whether suffering from psychoses or not.

There are other practical advantages which would accrue from treating acute curable psychoses in general hospitals. Physicians in attendance would unlearn the old fallacy that disease manifested itself either by mental or physical symptoms and would learn instead that it exhibited both kinds of symptoms; they would learn a saner, broader and more comprehensive conception of disease; psychiatry would be recognized to be what it really is — an intimate part of clinical or internal medicine. . . . It is a practical illustration in concrete form of the argument advanced in this paper."

Henry[48], in 1929, critically reviewed the case histories of 300 neuropsychiatric patients seen in the medical and surgical wards of the general hospitals of New York City and drew several conclusions, among them: "All general hospitals should have a psychopathic department and at least one attending psychiatrist." Gayle[49] in 1951, is hopeful that general hospitals are becoming "general in reality." Collier[50], in 1931, asked whether our general hospitals are doing their duty in the care of psychiatric patients, and stressed the need of lightening the load of our state institutions. His point of view is still very applicable. Farrar[51], addressing the annual convention of the Ontario Hospital Association in 1931, stressed the importance of "Dispensing with legal formalities" in admitting patients to general hospitals. Wilson[52], Medical Director of John Sealy Hospital in 1938, asked: "Can a hospital truly be classified as a general hospital when it limits its admissions only to medical, surgical, and obstetrical patients and does not provide facilities for the care of a vast number of the more common types of illness." Hamilton[53], in 1938, declared: "Psychiatry is a branch of medicine that has not been especially welcome in the general hospital. It is commonly expected that one psychiatric patient will squirm and grimace, another will be noisy and a third will commit suicide. We may retort that since the epidemic of encephalitis

we have become tolerant of the person who grimaces and squirms; that the children's service and the obstetric service are much noisier than any psychiatric service; and that in spite of a very vigorous policy of applying mechanical restraint and using huge doses of sedatives when an abnomral mental condition is found among patients in medical and surgical wards, nevertheless suicides occur there."

The hysteriac bids for sympathy, attention, understanding, and extends his desire "to belong" to the rest of the human herd; the psychotic is less vocal, but probably thinks no less as he is certified to be confined within the cold walls of locked doors and encased windows, final proof to him of his "rejection" by the rest of us. A patient with known psychiatric symptoms still is more readily admitted to a jail than to a general hospital. This is not as it should be in our days of culture and vaunted civilization. It is hoped that public education and public relationships will foster progressively a more wholesome understanding of the psychiatric patient and his needs.

Many bridges of understanding must still be built before general hospital personnel, medical and lay alike, will have removed segregation, incarceration, and fearsome surveillance from the care of the mentally ill.

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RIGID WIRE FIXATION OF FRACTURES OF THE HAND

W. D. Butt, M.D.*

For many years fractures of the hand have been successfully treated by wrapping the hand in position of function or immobilizing the hand with the aid of plaster. The great percentage of fractures is still treated in this manner, but with the advent of internal fixation of fractures, a similar method has evolved using Kirschner wires for the small bones of the hand. The wires may be inserted successfully longitudinally, transversely or obliquely.

Insertion of Kirschner wires may be done with a Steinman pin inserter. This instrument is used in the manner of a wood worker's awl, in a back and forth rotary motion. The drill, designed by Dr. Bunnell, provides a more satisfactory insertion of the wire but demands that both hands of the operator be employed in handling the drill, and an assistant must keep the fragments accurately approximated.

The Dingman Lion jaw forceps, for holding small bones, are effective in open reduction. The 'end on' wire cutter provides a method for cutting the wire close to the skin, which will then retract over the wire. If the wire is allowed to protrude, it may be removed more easily, but the opening in the skin provides an entrance for bacteria. Antibiotics provide the protection from infection which is a common sequelae of introducing a foreign body into bone.

Adequate operating room x-ray must be available, and the fractures may be reduced either open or closed. The anesthesia can usually be obtained regionally with a metacarpal or brachial block. Seldom is general anesthesia necessary, but the use of a pneumatic tourniquet is essential for good open reduction.

The wire must be started at right angles to the cortex of the bone, and then directed as desired. These wires differ from Kuntchner nails which obtain their stability from filling the medullary cavity. Rush and Lottes nails have a "spring" force binding the fracture site by impinging all three points on the internal aspect of cortical bone.

When sufficient callus has formed to hold the fracture the wire is removed, and gentle active motion begun. Several authors state that no joint disability follows, but if the extensor expansion has been immobilized some limitation of motion occurs. In the older age groups frequently traumatic arthritis develops when joint surfaces are traversed.

Compound fractures can generally be debrided, reduced and immobilized with a K wire, and the wound closed. The patient must receive adequate doses of antibiotics.

If there is loss of covering tissue or the wound is several days old, soft tissue coverage must be obtained first. The wound must be cleansed and allowed to heal before open reduction and fixation of the fracture.

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*Division of Plastic Surgery

A great advantage of internal fixation is that early motion of all joints not involved in the fracture may be obtained. Frequently, with transverse and oblique pinning, active motion may be started immediately as in the transverse wiring of metacarpals.

There are certain elective procedures such as arthrodesis of joints which are well handled with the aid of a transfixing wire.

Dr. Bunnell[1] and Sir Reginald Watson-Jones[2] feel that a Bennett's fracture can be held until healed by a K wire. The transposition of a metacarpal ray may be immobilized with a K wire as in moving the fifth to the fourth position when there is loss of the ring ray. Bone grafts can be properly positioned and held with either single or crossed rigid wires.

The following series of pictures illustrate the material discussed.

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The author expresses appreciation to Dr. R. Clifford and the Photography Department for assistance in the preparation of this paper.

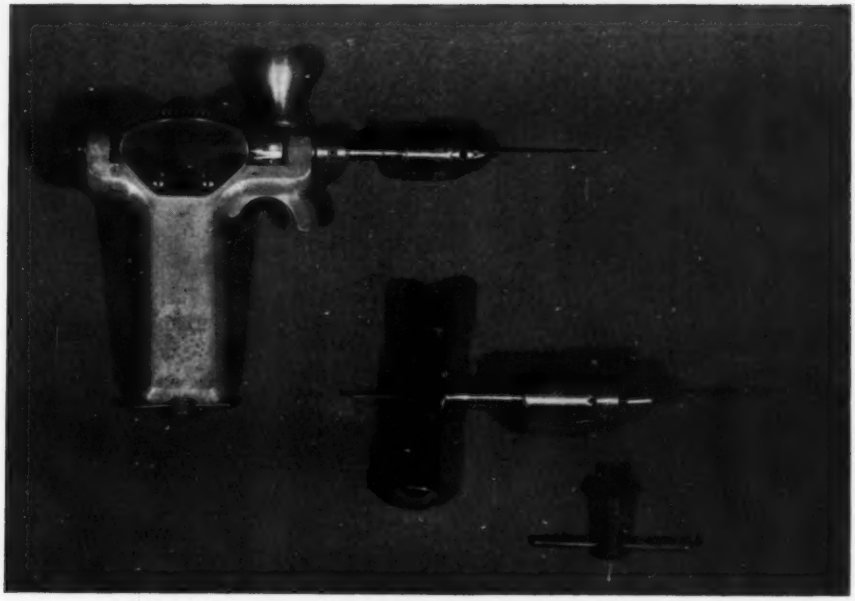

Figure 1
A. Steinman Pin Inserter (Awl principle). B. Bunnell Hand Drill.

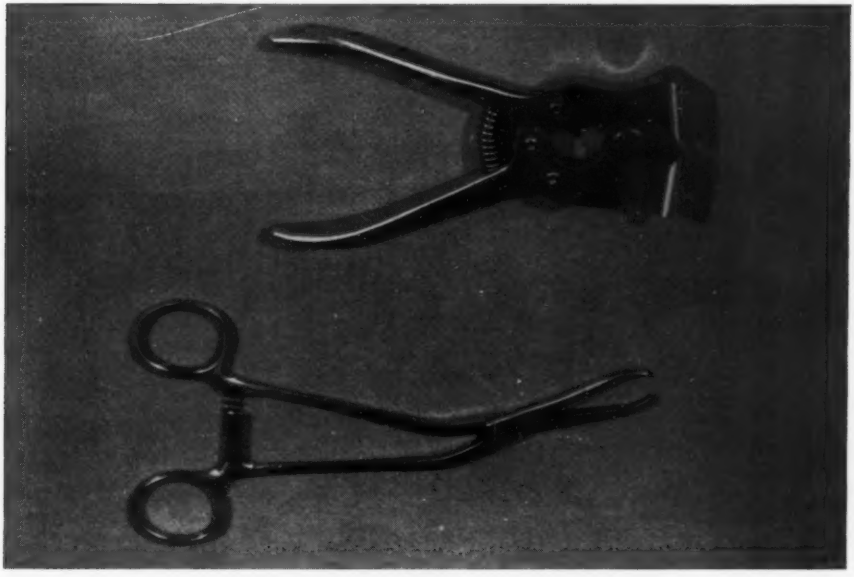

Figure 2
A. "End On" Wire Cutters. B. Dingman Bone Holding Forceps.

Fig. 3 Typical "baseball" finger tip, two months old. Open reattachment of extensor tendon. Immobilized in hyperextension with K wire passing through distal interphalangeal joint and missing proximal interphalangeal joint, but secured into proximal phalanx.

Fig. 4 Non union middle phalanx of ring finger. Banked bone graft immobilized with crossed wires. No movement of fragments, but no callus formation.
Four months later autogenous bone graft removing proximal fragment of middle phalanx.

Fig. 5a. Fracture of proximal phalanx of left little finger with rotation of distal fragment at right angles to proximal shaft. — Stiffness of joint one month post op. — Good motion in two months.

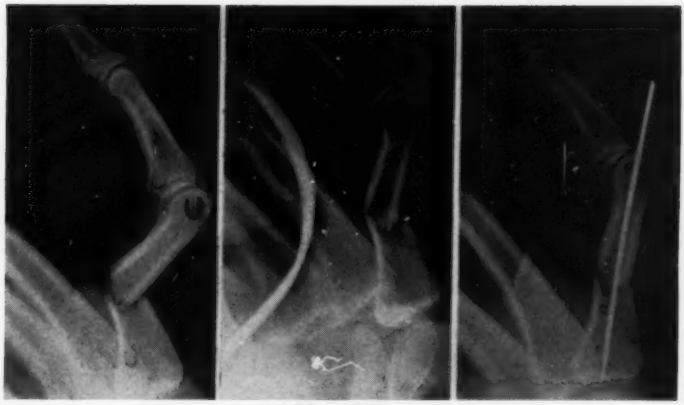

Figure 5b

Closed reduction of proximal phalanx of left finfer. *Open* reduction one month after accident. Fixation with intramedullary wire. Minamal stiffness in two months of proximal interphalangeal joint.

Figure 6

Three week old fracture of proximal phalanx, left little finger. Diagonal Kirschner Wire, proximal interphalangeal joint and M.P. joint movable.
Three weeks later limitation of P.I.P. joint of 60°. Two months, 40° limitation of motion.

Figure 7

Fracture of mid shaft of second metacarpal. Open reduction and intramedullary longitudinal wire fixation. Wire removed in one month; some stiffness. Good motion in two months.

Figure 8

Fracture with volar displacement of head, fifth metacarpal. Closed reduction unsuccessful, fibrous union destroyed with an osteotome; and satisfactory alignment with a K wire.
No tenderness and good motion one month post op.

Figure 9

Open reduction of head of fifth metacarpal. Immobilized with two transverse wires. Motion of M.P. joint immediately post. op. Wires were removed in three weeks.
One month slight limitation of motion at m.p. joint.

Figure 10a

Compound fracture of tuft of thumb. Alignment with K wire wounds sutured.
Pin removed in one month, and in six weeks patient was using thumb satisfactorily.

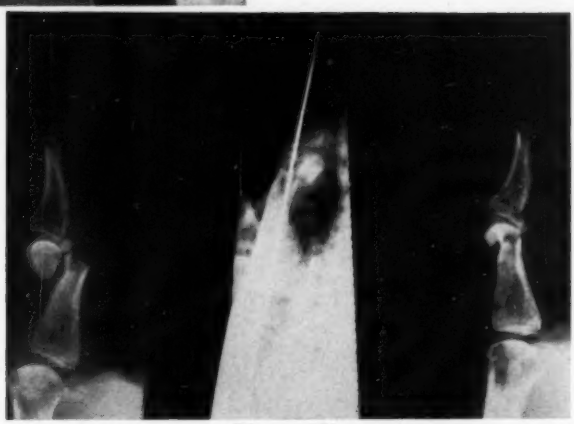

Figure 10b

Two months post trauma, mal union of proximal phalanx of thumb. Open reduction with removal of fibrous tissue.
Aligned with K wire and immobilized with plaster. Wire removed in one month. Good function in three months.

Figure 10c

Open reduction of a three day old compound fracture of proximal phalanx of thumb. Immobilized with crossed wires and circular braided wire. Removed wires due to infection six weeks later, secondary operation. Similar crossed wire immobilization, and satisfactory function obtained.

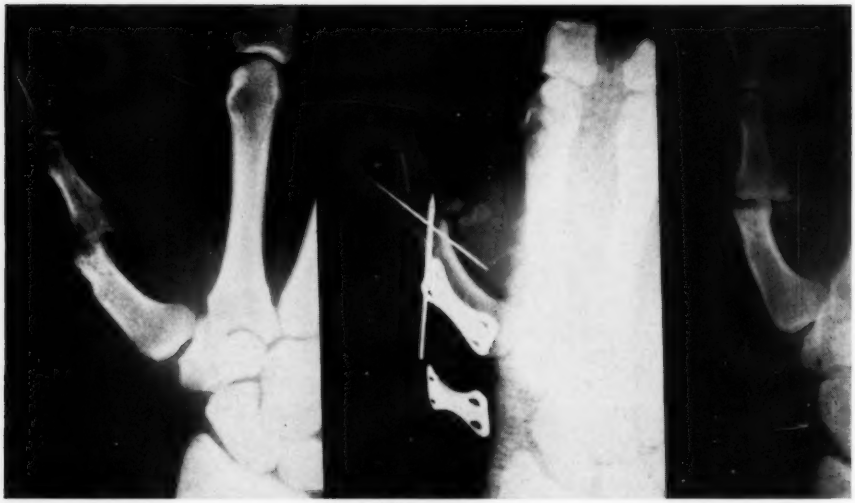

Figure 11

Compounded saw injury removing head of first metacarpal. Fusion of M.P. joint with aid of K wire. Good function of thumb, playing baseball three months later.

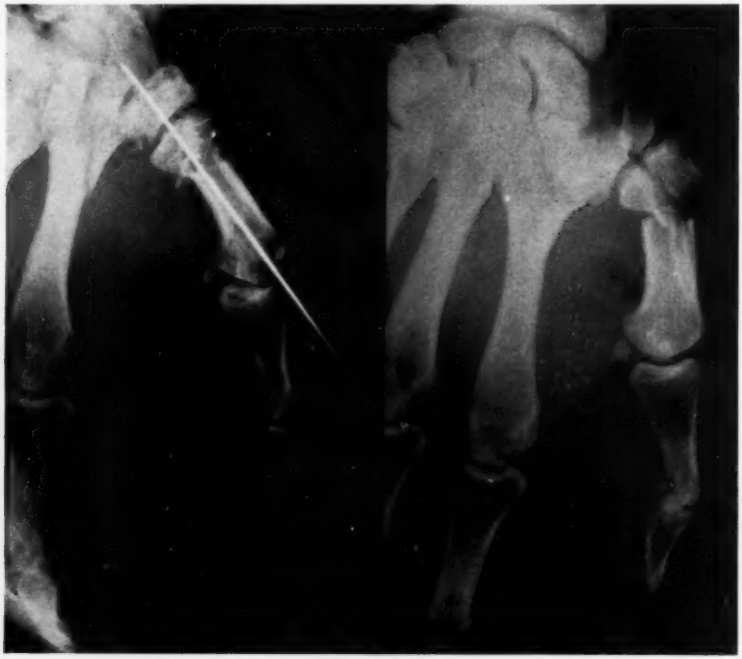

Figure 12

Compound comminuted fracture of the base of the first phalanx. Open reduction with K wire stabilization. Fragments immobilized with braided 5.0 wire.
Wire removed five weeks later. Capsulotomy, three months later.

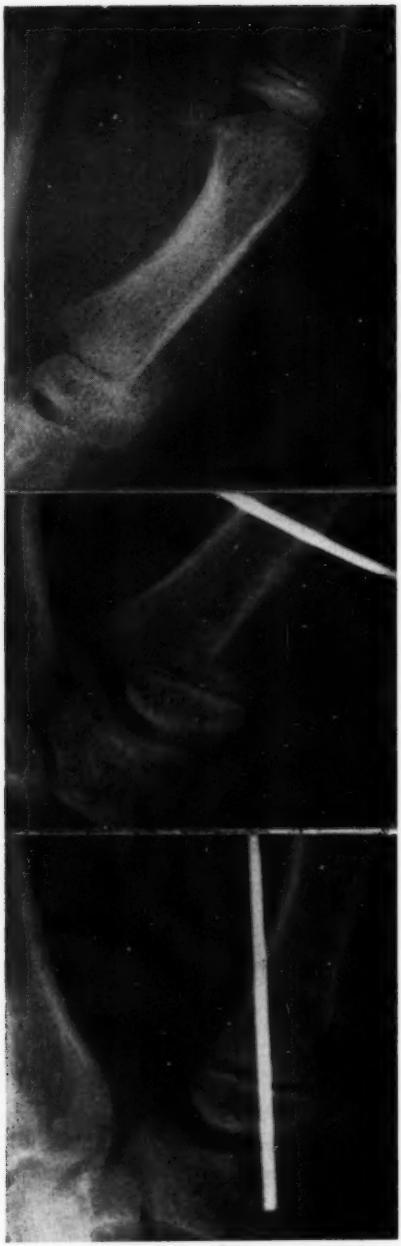

Figure 13

Fracture dislocation of epiphysis of first metacarpal. Attempted closed reduction with transverse wire unsuccessful. Open reduction at carpo-metacarpal joint, with fixation of epiphysis; joint not involved.

Good function one month. Wire removed in situ for six weeks.

Figure 14

Compound injury to first M.P. and carpal bones, subsequent osteomyelitis. Thumb fused in abduction. Op., opened scar tissue, and inserted bone block between first and second metacarpal, thumb in position of function.

THE USE OF RADIOACTIVE GOLD IN THE TREATMENT OF CANCER OF THE CERVIX

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L. E. PREUSS, M.S.**

The cure of metastatic malignancy by surgical extirpation, radiation therapy, or a combination of the two has achieved only limited success. Few patients are saved by operation when the lymph nodes contain cancer cells. Recurrences in irradiated patients are frequent. The implication seems to be that viable tumor cells are present outside the limits of surgical extirpation and beyond the bounds of effective irradiation. Better results can only be achieved by more extensive surgery or by radiation. Radical surgery is probably approaching its limit. Treatment with chemotherapeutic agents has thus far been discouraging. New and improved methods of radiation seem to offer the best chance of increasing survival figures.

In radiological therapeutics the cancericidal effect is produced by means of tissue ionization. The limits of tolerance of normal tissue to externally applied gamma and x-irradiation have been the chief therapeutic barrier. The development of supravoltage x-ray machines and the substitution of $Cobalt^{60}$ as a source of radiant energy have resulted in a more uniform depth dose but have not increased the tolerance of normal tissues to radiation. Unfortunately, during the procedure of radiation, normal tissues cannot completely be dissected or positioned out of the path of the radiant energy.

The development of the pile as a source of energy characterized by the intense neutron flux has resulted in the development of a number of beta emitting radioactive isotopes. Therapeutically, radioactive colloidal gold is being used with increasing frequency. Its empirical record has been encouraging.

Radioactive gold possesses certain properties that make it an effective agent for interstitial injection:

1. The colloidal particles are eagerly ingested by macrophages.
2. 95 percent of the tissue ionization produced originates with the beta radiation. Radiation consists of three beta and three gamma rays. The 0.290 Mev gamma and 0.963 Mev beta make up about 99 percent of the decay scheme.
3. The half-life is 2.69 days and 94 percent of the radiation dose is delivered within the first eleven days.
4. The maximum range of the 0.963 Mev beta radiation is 3.8 mm in tissue.
5. The colloidal gold particles are basically inert.

The principle of depositing a high energy source in the form of colloidal particles in the same locus as the tumor cells, namely, the regional lymph nodes is quite different from external radiation in which the effectiveness is proportionately diminished by linear distance.

Radioactive gold as a trillion point source of beta radiation has had increasing clinical use for the treatment of malignancy. One of the most encouraging developments has been in the treatment of women with cancer of the cervix. The results of this type of therapy reported by Allen[1] have been encouraging. Radioactive gold is used in

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conjunction with radium and often surgery. The function of the radioactive gold is to destroy the metastatic tumor in the broad ligaments and regional lymph nodes.

METHODS

Radioactive gold is injected into the broad ligament region in volumes of 35 cc on each side aimed at three sites — obturator, hypogastric and paracervical. The amount of radiation employed has been 50 mc in each parametria. Care is taken in the handling of the material. Spillage and contact with the skin is avoided. Within 72 hours the patient is discharged from the hospital.

DISTRIBUTION

In suitable patients Wertheim hysterectomy and pelvic node dissection is usually carried out 6 to 8 weeks after the injection of the radioactive gold. The radioactive gold has been employed at the Henry Ford Hospital for the past 18 months. During that period of time 15 cases have received radioactive gold. Nodes removed at time of operation universally were black in color indicating the presence of radioactive gold. Micropathological examination revealed aggregates of gold to be present in the nodes with the greatest concentration to be seen in the periphery of the node. Calculation of the amount of radiation in terms of reps delivered to the nodes per gram of tissue

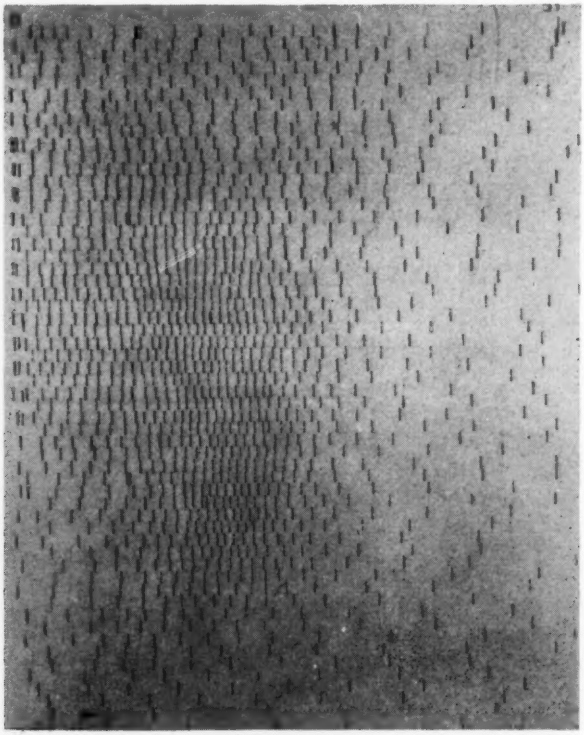

Figure 1

Scintogram of typical distribution of radiation over the left broad ligament.

has been determined by Allen[2]. The doses usually exceeded what is considered to be cancericidal. Scintograms were performed on 7 patients. Figure I shows a very typical distribution of radiation over the left broad ligament area in one patient. All tracings showed the gold to be evenly distributed in the broad ligament regions. Investigators in this field concur that the colloidal particles are picked up by the macrophages and deposited in the regional lymph nodes. Our experimental work with rabbits reveals that homogeneous interstitial injection of colloidal gold results in the homogeneous distribution of particles in the regional lymph nodes*.

Approximately 50 percent of the radioactive gold is removed at operation indicating the remainder migrates beyond the bounds of the operation. This migration to succeeding nodes is substantiated in the work on rabbits since time-concentration curves of a particular node show a very definite peak. This is, of course, desirable. Less than 1 percent enters the blood stream.

RESULTS

The potentiality of treating the regional lymphatics with radioactive colloidal gold in carcinoma of the cervix was first investigated by Sherman, Nolan, and Allen[3]. The recent report of Allen[1] using colloidal gold in the treatment of carcinoma of the cervix bears mention. The work has now been in progress for six and one-half years. The survival rates obtained in the gold series are shown in Table I, II, III. Radiogold has been employed in the treatment of cervical malignancy at Henry Ford Hospital for the past 18 months. Fifteen cases have received parametrial gold. The cases according to stage disease (League of Nations) are shown in Table IV.

STAGE I

X-ray and Radium				Au^{198} / Radium + / − Wertheim			
No. Treated		Alive without Disease		No. Treated		Alive without Disease	
		No.	Percent			No.	Percent
Total	35	26	74.2	87		79	90.8

Table I

Survival rates obtained in a series of Stage I cancer of the cervix patients treated with radioactive gold, radium and Wertheim hysterectomy compared with patients treated with conventional x-ray therapy and radium are shown above. In a small percentage of cases additional radium was given in lieu of Werthdeim hysterectomy.

*Work to be published

STAGE II

X-ray and Radium				Au^{198} / Radium + / − Wertheim			
No. Treated		Alive without Disease		No. Treated		Alive without Disease	
		No.	Percent			No.	Percent
Total	69	38	55.1	62		55	88.7

Table II

Survival rates obtained in a series of Stage II cancer of the cervix patients treated with radioactive gold, radium and Wertheim hysterectomy compared with patients treated with conventional x-ray therapy and radium are shown above. In a small percentage of cases additional radium was given in lieu of Wertheim hysterectomy.

STAGE III

X-ray and Radium				Au^{198} / Radium + / − Wertheim			
No. Treated		Alive without Disease		No. Treated		Alive without Disease	
		No.	Percent			No.	Percent
Total	48	13	27.1	27		16	59.2

Table III

Survival rates obtained in a series of Stage III cancer of the cervix patients treated with radioactive gold and radium compared with patients treated with conventional x-ray therapy and radium are shown above. In a small percentage of cases Wertheim hysterectomy was also performed in the radioactive gold series.

Stage	No. Cases
I	6
II	6
III	3
IV	0

Table IV

Fifteen Cases Treated by Parametrial Radioactive Gold, according to Stage of Cancer. (League of Nations). Nine operated. One death.

Fourteen of the 15 cases are alive without disease. One patient, a League of Nations Stage II, developed distant metastases in the lungs and liver. At the time of her demise the pelvis was free of palpable tumor, and both ureters were unobstructed. It seems likely that distant metastases were present at the time of the initial therapy. Our figures suggest that we can perhaps approach the results obtained by Allen and Sherman.

One of the most significant features of the series has been the absence of recognizable tumor in the lymph nodes removed at operation. Of the 15 cases, 9 were operated. Of the 9 cases, 4 were classified as Stage I, 3 as Stage II, and 2 as Stage III. Meigs[4] found positive nodes in 18 percent of the Stage I cases, and 45 percent positive nodes in the Stage II cases (4). No figures on Stage III cases were presented. Of the 9 cases operated, only one, a Stage III case, demonstrated recognizable tumor cells in a lymph node, and this was considered to be radiated tumor. Approximately 15 months after treatment this patient is alive without evidence of disease.

COMPLICATIONS

The most frequent complication produced by gold therapy is leg pain. This pain occurs from two to four weeks following therapy. Of the 15 cases treated with radiogold, 6 developed leg pain. The pain lasted from three to six months, but has cleared in all cases. The distribution of leg pain suggests sacral nerve root involvement. One patient developed a transient saddle block type of anesthesia.

Liver function studies were performed on three patients. No significant change from normal was observed. No ureteral, bladder, or bowl fistulas developed. No anemias or leukopenias secondary to radioactive gold were noted.

SUMMARY AND CONCLUSIONS

Homogeneous distribution of colloidal gold in the regional lymph nodes is accomplished by homogeneous interstitial injection of the colloidal suspension. The deposition of a trillion point source at the site of tumor metastasis results in tumor destruction in this area. In the case of large collections of tumor cells, radioactive gold does not effect the inner portion of that mass. The removal of such a mass must be performed by surgery. Fortunately, in the case of cancer of the cervix, nodes found to be completely replaced by tumor occurs as a very late development in the course of the disease, but the infinite number of lymphatic pathways and regional lymph nodes which have been sprinkled with cells can be eradicated by radioactive colloidal gold.

The encouraging survival figures which are being obtained by the use of radioactive gold in the treatment of cancer of the cervix attest to this fact. Fourteen of the 15 cases of cancer of the cervix treated in the past 18 months at Henry Ford Hospital with radioactive gold, radium, and surgery are alive without evidence of disease. Nine cases were operated. One showed recognizable tumor in lymph nodes removed at operation. The chief complication was leg pain.

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PROBLEMS IN ADRENAL STEROID THERAPY

Medical Staff Conference

J. G. MATEER, M.D., Physician-in-Chief

Panel

R. W. SMITH, JR., M.D.[1] J. W. KEYES, M.D.[4]
D. C. ENSIGN, M.D.[2] J. H. SHAFFER, M.D.[5]
R. W. MONTO, M.D.[3] C. S. LIVINGOOD, M.D.[6]
R. C. MELLINGER, M.D.[1]

Dr. Smith: The rapid development in basic steroid chemistry and in the commercial preparation of various therapeutic derivatives, with the inevitable flood of proprietaries, has led to considerable confusion for the practicing physician. It is apparent that we cannot discuss, in the short time at our disposal this morning, the indications for steroid therapy in the many areas of internal medicine and surgery. Accordingly, we will limit the discussion to the comparative properties of the various steroids, certain adjuvants of therapy and the ways in which the various specialties of the Hospital are presently using these materials.

It is logical to begin by commenting on the comparative properties of the corticosteroids which now are being used widely in clinical practice. These are listed in Table I. In order to compare their respective properties, hydrocortisone has been selected as the reference point, inasmuch as it is now recognized as the naturally occurring corticosteroid of greatest physiological significance. This is not to overlook the potential clinical importance of aldosterone but since this mineralocorticoid has no immediate therapeutic role it will be referred to only in passing. Hydrocortisone has been arbitrarily assigned a potency rating of 10 in each of the 4 physiological properties compared. The various steroids have been rated according to their effects on electrolyte excretion, carbohydrate metabolism, inflammation and ACTH suppression. The latter, as most of you know, refers to the property of a steroid to inhibit the synthesis or the release of corticotropin by the pituitary, which inhibition in turn results in the arrest of adrenocortical activity and leads ultimately to cortical involution. One point of importance is that with all the steroids listed, the anti-inflammatory or therapeutic effects and the ACTH-suppression effects run essentially parallel. So far, the organic chemists have been unable to divorce the anti-inflammatory action from the antianabolic or carbohydrate regulating action. This is a point often not appreciated by many practicing physicians. The tendency is to say, "Well, inasmuch as a steroid has less sodium-retaining action, it is safer." Its other properties are overlooked. If we are to use the newer derivatives in practice we must realize that

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This is an edited report of a current conference of the Department of Medicine of the Henry Ford Hospital.

1 Division of Endocrinology
2 Division of Arthritis
3 Division of Hematology
4 Division of Cardiology
5 Division of Allergy
6 Division of Dermatology

there will be more potent effects on carbohydrate metabolism and on adrenal involution.

Dr. Ensign will say a few words about the many aliases that surround the delta derivatives, prednisone and prednisolone. The double bond in ring A, which distinguishes these steroids from their parent compounds, has not altered the relative potencies of the two. Since the overall potency enhancement of both has been so great, in the order of from 3 to 5-fold, the dosage difference for the two is, milligram-wise, quite small and possibly will not be heeded as clinically significant. This is one of the inherent dangers of enhancing potencies. The physician who once was impressed by the 50 mg. dose difference between 200 mg. of cortisone and 150 mg. of hydrocortisone, these being pharmacologically comparable, might not readily appreciate the differences between 40 and 30 mg. of prednisone and prednisolone, respectively.

The potencies of the halogenated steroids are well recognized. However, they have not been used widely for parenteral therapy due to the striking enhancement of the sodium-retaining action. Fluorohydrocortisone, for example, is also potent in respect to the other properties listed and the chief clinical value, apart from its topical use, is its ability to inhibit the adrenal cortex without yielding significant amounts of urinary 17-ketosteroids to confuse the measure of endogenous ketosteroid production. This applies even more to the fluoro derivative of prednisone. Perhaps the real significance of fluorohydrocortisone is the fact that it heralds a promising man-made chemical phenomenon, for there is early evidence that halogenation of other, non-adrenal steroids may potentiate their respective physiological properties.

Only early observations have been made on the biological potencies of the halogenated derivatives of prednisone and prednisolone. I have question marks in the table because this slide (Table 1) was made some eight months ago. The potencies may be a little nearer to that of fluorohydrocortisone than the 50 times hydrocortisone as listed. They are probably nearer 25 or 30 times hydrocortisone but I have had no extensive experience with the compounds.

TABLE I

COMPARATIVE ACTIVITIES OF THE ADRENAL STEROIDS

	Sodium Retention	Anti-inflammation	CHO Effect	ACTH Suppression
Aldosterone	1500	0	0	0
F-Hydrocortisone	1000	250	250	250
DOCA	50	0	0	0
Hydrocortisone	10	10	10	10
Cortisone	8	8	8	8
Prednisone	12	32	32	32
Prednisolone	15	40	40	40
F-Prednisolone	250?	500?	500?	500?

This brief and general review of comparative properties permits us to turn to the next and perhaps even more confusing aspect which is the nature and names of the

many proprietary preparations now on the drug market. Dr. Ensign has been kind enough to agree to bring some sense out of this apparent turmoil.

Dr. Ensign: It is a turmoil all right, as this batch of sheets will indicate, torn from the last issue of one of the throw-away medical magazines. These are just the ads that had to do with the steroids in this last month's issue. In spite of the great numbers of pages involved they pertain to just about two products. The confusing thing, of course, is that these drugs were released before being given official designations at the American Rheumatism Association Meeting. The names used first were not the more chemical terms which were finally adopted. The fortunate company that released its product to the market first in commercial quantities chose the catchy name of Metacorten*, which is what most people think of as the representative of this steroid group. The official name that was later selected is a somewhat more difficult one to pronounce and to remember, namely, prednisone. I think physicians are getting used to it. Prednisone and prednisolone are the official designations for the delta derivatives of cortisone and hydrocortisone, respectively. Prednisone is marketed under the names Metacorten*, Deltra*, and Deltrasone*. It is present in Cordex*, which is one of the several "super" aspirins. It is presented in a buffered form with aluminum hydroxide and magnesium trisilicate as Co-Deltra*. In the prednisolone group we have Metacortelone*, Hydeltra*, Delta-Cortef* and Sterane*, which are often advertised as the most potent anti-rheumatics. Prednisolone is marketed in a buffered form under the names of Co-Hydeltra*. Prednisolone is the chief ingredient of the "super" aspirin put out by another company under the name of Sigmagen*. I think the deceptive aspect is that most of these advertisements speak about drug safety. If one takes the time, however, to read the little circular incorporated in the package, he finds that the same precautions have to be used and that the same side effects can occur as with cortisone and hydrocortisone. After all, these are very potent steroids. True, they are roughly four times as potent in their anti-inflammatory effects as our older friends, cortisone and hydrocortisone, but they are also four times as dangerous in some of the side effects. Even though activity is less with respect to sodium retention, this can still be a problem. The chief point in taking this much time is to make emphatically clear that behind all the new names we really have only two practical new steroids, namely, prednisone and prednisolone. They are extremely useful drugs in given situations but their use is fraught with the same dangers attending cortisone and hydrocortisone therapy.

Dr. Smith: Thanks very much, Dr. Ensign. The panel spent some time in preparing questions to best cover the subject of the hour, which is *how* we are using these preparations and not *why*. Which agents do we select? What are the therapeutic programs and what are we encountering as to side effects? These are to be answered in the light of experience by representatives of divisions of the Hospital. It was interesting to see how the thinking went. The first question to come up almost immediately from several quarters was: "Is there any basis for the preferential use of one or another of the parent compounds or their derivatives?" This is a question which we might direct to Dr. Ensign first since he has been so kind as to open the discussion.

Dr. Ensign: First of all, just to make myself clear and not to indicate that I am

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advocating these drugs as a "cure" for arthritis, I might show you the outline of our current therapy for rheumatoid arthritis. Our basic program which has been a development over many years has been unaltered by the appearance of these new drugs. All of the steroids, both the old and the new, are used only as supplemental

OUTLINE OF TREATMENT OF RHEUMATOID ARTHRITIS

BASIC PROGRAM

Orientation of Patient and Family

Diagnosis
Nature and course of disease
— no known cause, hence no "cure"
— but some relief possible for all
— a long term (usually life-long) program

Objective of treatment

— relieve symptoms
— improve general health level
— prevent crippling
— arrest disease if possible
— improve function of damaged joints
— educate patient in adjusting to any uncorrectable residuals.

Symptomatic Therapy

Rest
— mental
— physical
— local — splints in actue stage, with joints in optimal position
Aspirin or sodium salicylate to tolerance
Codeine — if necessary for pain relief during night

General Measures

Correct or improve personal and environmental stress factors wherever possible
Provide adequate diet
— supplemental vitamins or minerals if indicated
Insure proper elimination
Remove obvious focal infection
— antibiotics prophylactically
Rest — continuing definite program
— frequent rest periods preferable
— correct faulty joint positions
— proper supports if necessary

Local Measures

Corrective exercises
— detailed program
— all joints, through maximum range of motion
— daily, repeated several times, increasing as tolerated
Other physical therapeutic measures
— heat, dry or moist
— massage — avoiding tender joints
Joint aspiration and intra-articular hydrocortisone TBA — selected cases

Medications

Aspirin (or sodium salicylate)
— regular maintenance dosage
— enteric coated or buffered
Sedatives
Codeine
— sparingly for severe pain
— avoid other narcotics

SUPPLEMENTAL PROGRAM (Useful *only* as additions to basic program)

Special Measures

Gold salts
— Best available "stopping mechanism"
— Safe if used with due precautions under direct personal supervision of physician
Steroids and hormones
— cortisone
— hydrocortisone
— newer synthetic steroids
— ACTH
Phenylbutazone — if effective and well tolerated
Blood transfusions
Change of climate

Reconstructive Measures

Surgical correction
Rehabilitation
— physical therapy
— occupational therapy
— devices to aid the use of handicapped joints

measures in selected cases. I think that we are undoubtedly using more of the newer preparations than we are of hydrocortisone in the long-term care of the patients who are receiving the steroids. We do not use steroids in every patient with rheumatoid arthritis; however, we are still using hydrocortisone in those who were started on it and have been taking it without appreciable side effects. One of our reasons for using more of the newer agents is to find out more about their properties, particularly as to whether the buffer coating which is offered gives any greater protection against some side effects. If I were treating a new patient and were not trying to learn more about the newer steroids, I probably would use hydrocortisone first. If the patient did well on a moderate or small dose and was not having any appreciable side effects, the hydrocortisone would be continued. If there were difficulty with sodium retention, I would naturally switch to one of the newer compounds. In our experience there is not much to choose between prednisone and prednisolone, with the exception that we do find the odd patient who apparently tolerates one better than the other or who responds to one better than to the other. Yet, there is nothing consistent about it to enable us to choose between the two.

Dr. Smith: Why would you start with hydrocortisone in preference to one of the newer agents?

Dr. Ensign: Because we know more about it and we have been working with it for a good many years. It is the naturally-occurring hormone of the adrenal gland. I think that when it works, it works as well as any other.

Dr. Smith: Perhaps Dr. Monto would like to say something about his experiences with the various steroids and whether he has any preference for one or another.

Dr. Monto: The steroids are the hematologist's best friend and the closest to our heart is cortisone. We find these agents extremely useful in the management of the lymphomas and leukemias, in the hypoplastic states of bone marrow, as well as in idiopathic thrombocytopenic purpura. Perhaps my thesis is best illustrated by brief comments on a group of patients with idiopathic thrombocytopenic purpura. A regularly encountered response to steroid therapy in thrombocytopenic purpura, whether the latter is secondary or idiopathic, is the very prompt rise in platelet counts.

In one particular patient on about 80 mg. of hydrocortisone daily, however, there was an inadequate platelet response. The dosage was doubled without a further change. When cortisone in doses of 300-400 mg. was administered, we then noted a fair response. Another patient received prednisone at a level of 40 and later 80 mg. a day. There was no appreciable response. With 200 mg. of cortisone daily, however, a satisfactory effect was obtained and since this patient was an adult, splenectomy was done when we reached platelet levels of 150,000. There are exceptions, however, and cortisone may give only a temporary and inadequate response.

Dr. Smith: Would you say from this experience, Dr. Monto, that you would advise others not to begin therapy with hydrocortisone or prednisolone?

Dr. Monto: Yes, I feel very strongly that cortisone is the agent of choice. There is something peculiar about the hematopoetic tissue. Perhaps it is the lack of anti-inflammatory response that makes it different. We feel that cortisone is not only a stimulus for the various cell groups in the bone marrow but it also has a specific action upon the terminal vascular bed which is beneficial in the group of patients which we encounter.

Dr. Smith: Is this the general consensus in hematological practice?

Dr. Monto: Yes.

Dr. Smith: Dr. Keyes, perhaps you would like to comment on whether you feel there is some basis for the selective use of one or another of these steroids in the rheumatic fever problem.

Dr. Keyes: I would first like to make one point clear. All the members of this panel probably use these steroids many more times than do we. Where we have encountered acute inflammatory disease, however, such as in acute carditis, we have used cortisone probably to the greatest extent, simply because of the few cases that have reached us since the acceptance of the newer derivatives. Our experience with prednisone has been rather small. It would seem, however, that the preference of prednisone over cortisone would be determined mainly by whether or not you are concerned that sodium retention is going to be a factor in the outcome of the treatment. In the absence of congestive failure or imminent congestive failure I believe cortisone will give as satisfactory a response. The newer preparations should be used if there is any cardiac failure or if you suspect that sodium retention is already occurring.

Dr. Smith: Before passing on to hear what Dr. Shaffer is using in his allergy practice, I should like to make one comment. Increasing the potency of a pure drug from 10 to 100 times, let us say, in itself is not a strong justification for its selective use. Even if aspirin were ten times more potent, it would not necessarily be a better drug. The primary advantage that has come from the discovery of prednisone and prednisolone is, of course, in having corticoids of lower sodium-retaining potencies. As I mentioned briefly in the opening comments, there is a tremendous amount of false security in the minds of practitioners because they have heard that these agents have *fewer side effects*. It must be kept in mind that as we have increased the therapeutic potency five-fold, we have increased the chance for major side effects to the same degree.

Dr. Shaffer, do you have a particular preference for any one of the steroids in your allergy practice?

Dr. Shaffer: We use several of these preparations rather regularly but our preference

is for prednisolone. With 15 mg. of this steroid daily, we can control our patients very well and get the desired anti-inflammatory effect on an allergic type of reaction. In more severe cases, we may possibly use 20 mg. in a 24 hour period. In our experience, 3 or 4 days of therapy with that dosage level will give us the desired effect and then we can appropriately cut the dosage. We have some patients who are on a maintenance dose as low as 2.5 mg. per day. Since most of our patients are treated on an out-patient basis, the lack of sodium retention is very important for our particular group. We are very much aware of the other side effects and take steps to reduce them as much as possible. We have had considerable experience with hydrocortisone and continue to use it now. The intravenous form is helpful in severe allergic reactions where rapidly achieved high levels of steroid are needed. In such instances, 100 mg. of the free hydrocortisone in alcohol solution, given intravenously in 600 c.c. of glucose and water over a six to eight hour period, has been found satisfactory. On that type of therapy patients do well in a 24 hour period and may be practically symptom-free of severe allergic reactions, such as to serum or antibiotics. Our experiences with ACTH were among the first in the hospital. We use it now primarily to stimulate the adrenal gland at the end of a course of steroid therapy. Whether that is the correct technique or not, I do not know. I hope this point will be discussed today.

Dr. Smith: Yes, we will come to that in a few minutes. Briefly, would you say that there is general unanimity about the selective use of steroids in the field of allergy?

Dr. Shaffer: There is unanimity of opinion among the top flight allergists that one or another of the steroids is the last preparation to be used in treating an allergic individual. Unfortunately, it is the first and only thing that has been prescribed for many of the patients who later come to us. The most difficult patients we have to treat are those who have been given long-term cortisone therapy elsewhere for a year or so. They are very resistant to the usual measures, and since they continue to have allergic symptoms such therapy is certainly not the answer to the problem.

Dr. Smith: Dr. Livingood, it is said that dermatologists are using a sizeable fraction of the total steroid production in this country. Would you give us some ideas as to what preparations you are now using in the Dermatology Clinic and as to your preferences?

Dr. Livingood: Dr. Smith, dermatologists alone are not using all the steroids that are applied topically. This applies to such use by all physicians. As all of you know, topical steroid therapy, to a certain extent, has revolutionized the management of certain types of skin diseases. It has not replaced other time-honored remedies for these conditions but it certainly is here to stay. Cortisone has no effect whatsoever when applied topically except in the eye, as was first shown at this hospital, so we can dismiss that. Hydrocortisone was the first steroid to show therapeutic effects when applied topically, and even now it remains the agent of choice. Fluorohydrocortisone is about 10 times as potent in its topical effect but curiously enough one reaches a maximum effect. In other words, you do not increase the effectiveness of the fluorohydrocortisone significantly by increasing its strength above 0.25 percent. Roughly speaking, 2.5% hydrocortisone is equal to 0.25% fluorohydrocortisone and increasing the percentage of either does not increase their therapeutic effects significantly. The delta compounds have not been investigated thoroughly as to their effectiveness when applied topically, but the evidence to date would indicate that the effect of prednisolone

topically is roughly the same as the effect of hydrocortisone. We see an occasional patient who obtains a therapeutic effect with the delta compound and not with hydrocortisone but we also see instances which are the exact opposite. The same applies to fluorohydrocortisone. Occasionally we see patients who respond satisfactorily to fluorohydrocortisone and not to hydrocortisone. Again, sometimes it is the other way around.

Now, a word as to the percentage strengths of these compounds in the various preparations. The classical treatment when using topical steroid therapy is 1% hydrocortisone ointment. I should say that in as many as one of ten patients, increasing the concentration to 2.5% will assure a more satisfactory therapeutic result than with the 1% preparation. The great majority of patients, if they respond at all to such therapy, will respond to 1% concentrations. Decreasing the percentage strength to, say, 0.5 decreases the therapeutic effect in a very significant manner. It is true that some patients respond to 0.5% but, by and large, they do not.

The base used in the preparation makes a difference. Sometimes patients respond better when the hydrocortisone is incorporated in a grease or petrolatum type base, the base of Cortef®, for example, which is sold commercially. Sometimes patients respond better when a vanishing base or a lotion type base is used. An experienced dermatologist has an opportunity to select the right type of base and the optimum steroid concentration for the individual patient. Often, patients are helped by selecting the appropriate preparation, even though topical hydrocortisone previously was unsuccessful. What I am trying to say is that if one is to achieve the maximum therapeutic effect from this very potent topical agent, one must be prepared to run the gamut of the presently available preparations, using the three different types of bases and employing both fluorohydrocortisone and hydrocortisone. You might say, "Why don't you use fluorohydrocortisone exclusively if it seems to be just as effective in smaller doses?" Well, in the first place, the cost is about the same so you do not save anything by using smaller doses. In the second place, and this is the most important consideration, there is sufficient absorption of fluorohydrocortisone in some patients to result in a systemic effect and sodium retention. One is not obligated to consider the topical dosage of hydrocortisone if it does not exceed, say, 500 to a 1000 mg. a day. One must consider the topical dosage of fluorohydrocortisone, however, even when it is as low as 7 or 8 mg. per day in lotion form, because of this real danger of sodium retention.

Dr. Smith: Would you say, Dr. Livingood, that perhaps as much as 2-3% of topically applied hydrocortisone is absorbed, and that there is a rate limitation which is the reason we do not gain more therapeutically by increasing the potency of these preparations?

Dr. Livingood: Well, Dr. Smith, currently in our department we are making an effort to determine the exact percentage of hydrocortisone absorbed during topical application. Dr. Hildebrand and I are making these studies in conjunction with the physics department of the Upjohn Company which has supplied us with C^{14}-tagged Cortef®, (Upjohn Company hydrocortisone). It does appear, in preliminary experiments at least, that absorption is probably of the order of 2-4%, which is significant. There is also some work to show that when the hydrocortisone is applied to mucous membrane

areas, such as the perianal region, absorption is increased significantly and I think this must be taken into account.

Dr. Smith: Dr. Mellinger, we have not heard from you and I am wondering if you would comment briefly on the use of interval ACTH injections for patients on long-term steroid therapy in whom one wishes to maintain a reactive adrenal.

Dr. Mellinger: I do not believe there is a compelling reason to use interval ACTH for patients on long-term (adrenal-suppressive) therapy with any of these steroids. There is certainly no advantage to be gained by awakening the adrenal one day only to put it to sleep the next. There is small likelihood of maintaining an adrenal responsive to endogenous ACTH in patients receiving interval ACTH injections while on long-term adrenal suppressive doses of the steroids. I do not believe any of us would suggest this as a practical approach to the problem. When cortisone or any of the corticoids are to be discontinued, at that time there may well be reasons to use ACTH to achieve a responsive adrenal. The decision as to whether or not you will use ACTH at the end of steroid therapy will depend on such factors as the duration of the steroid therapy and the disease under treatment. Ordinarily, in a self-limited disorder that is over in three weeks, there would be no apparent reason to use ACTH at the termination of that therapy, simply because the adrenal-pituitary axis would not be sufficiently involuted to prevent its normal spontaneous activation. If one is treating a disease such as gout or asthma which might flare up during the steroid withdrawal period, then ACTH may well be given at the end of even a short period of steroid therapy. I would think that in any patient who has received steroids for a prolonged period, and by that I mean for 3 weeks or more, ACTH should be given at the termination of therapy until there is a reasonable demonstration that the adrenal is once more responsive to small amounts of ACTH.

Dr. Smith: Would you be willing to suggest a program as to the amounts of ACTH you would use at the end of, say, six months of prednisone therapy?

Dr. Mellinger: Before discontinuing the steroid therapy, I would begin ACTH in a dose of 40 units of the gel twice daily. Of course, you can vary this scheme according to your own experience. I think it is reasonable to maintain the ACTH therapy throughout the last 4 to 6 days of the tapering steroid therapy and perhaps the same number of days beyond. When using as large a dose as 80 units in 24 hours, there is little reason for continuing more than four days after cessation of steroid therapy. Even a patient with panhypopituitarism and long-standing adrenal involution is responsive within 48 hours to the latter ACTH stimulation. One can determine whether or not the adrenal is responsive to a lesser ACTH stimulus by appropriate tests but that actually would not be necessary in clinical practice.

Dr. Smith: One of the more important aspects of this topic is the problem of complications which are encountered in patients receiving prednisone and prednisolone. Do they differ from those experienced with the parent steroids? Dr. Ensign, do you have some ideas on this, particularly as to the problem of ulcers? What have you encountered?

Dr. Ensign: I have no specific data as yet but I am sure we are seeing more ulcers with the prednisone and prednisolone than we did with hydrocortisone. It may be a matter of relative dosage. It is quite disturbing to note the way these newer derivatives are being abused by the profession in general, lulled as we are by this feeling of false security which is unfortunately fostered by the advertisements. We

certainly are seeing everything in the way of side effects from these drugs that we ever saw with cortisone and hydrocortisone, with the exception of sodium retention. I feel as Dr. Shaffer does, that our biggest problem is weaning patients from such therapy.

Dr. Smith: Dr. Monto, have you had any problems with edema in patients receiving prednisone or prednisolone? We hear claims that they should not produce sodium and water retention but is this true to form?

Dr. Monto: Actually, I would willingly trade a little mooning of the face or some ankle edema for a remission in acute leukemia or a response in hypoplastic anemia. As I tried to point out in my opening remarks, I prefer cortisone to prednisone and for that reason have little experience with the latter to report. Our early results of therapy with these newer steroids were so poor that we quickly reverted to cortisone.

Dr. Smith: Associated with the problem of sodium and water retention is the problem of potassium loss. Dr. Keyes, would you make some comment as to whether or not we have to consider this problem in patients receiving prednisone or prednisolone?

Dr. Keyes: We do see rather severe potassium deficiencies. The experience in our own division with the newer derivatives is small, although we have had patients referred to us for electrocardiograms who have displayed evidences of hypokalemia, several, rather marked. Arrhythmias are a very common manifestation of hypokalemia, particularly ventricular extrasystoles. As far as our own routine practice is concerened, where large doses of any of the steroids are employed, supplemental potassium chloride therapy is prescribed in the dosage of 10 to 15 grains four times a day. It can become a real problem as Dr. Smith and Dr. Ensign have stated, particularly in the use of these more potent preparations. Where there is less sodium retention, there may be greater potassium excretion, simply because the catabolic effects are greater. It is a real problem and everyone should be aware of it.

Dr. Smith: With cortisone and hydrocortisone therapies we could protect against potassium loss to some extent by a rigorous restriction of sodium in the diet. Not only did we prevent or minimize the edema, but also we induced a lesser tendency for potassium excretion, although potassium supplements were still needed. With prednisone and prednisolone, there is not the problem of sodium retention, but this does not mean that the immediate potassium loss is not as great. Inasmuch as we have a more potent catabolic preparation, we have a real indication for the potassium supplements. I certainly agree that the level employed should be about what we use with cortisone and hydrocortisone, i.e., a gram four times a day.

Dr. Monto, do you have any other comments as to other supplementary measures you would prescribe for a patient receiving prednisone or prednisolone, or perhaps one of the parent steroids? What about the diet and sodium intake?

Dr. Monto: It has been our policy to use relatively large doses of corticoids for short periods of time and as a clinical remission is obtained to taper the steroid therapy accordingly. We operate then on the thesis that we should use the smallest possible maintenance dose and I think this has helped to avoid complications from some of the newer steroids. In addition to the potassium supplements, we have our patients routinely on diets containing 1 gram of salt.

Dr. Smith: Is that with the prednisone and prednisolone, as well?

Dr. Monto: Yes.

Dr. Smith: I wonder if the panel agrees that such salt restriction is necessary for patients receiving the newer derivatives.

Dr. Ensign: The patients we treat over many months are on relatively minor doses of these steroids. We have not been too strict about the salt restriction, certainly not as low as Dr. Monto mentioned. I always advise these patients to avoid excess salt and, if they develop any trouble, we do restrict, the intake of course.

Dr. Smith: The sentiment of a number of clinicians is that we need not go to 1 gram. Perhaps something can be said for a diet of no added salt. Excuse me for interrupting, Dr. Monto. You have some further comments.

Dr. Monto: Our patients are rather unique. Usually when we put them on steroids they remain on steroids until their demise. I think our problem is a little bit different from that of the rheumatologist and the allergist. Now, I would like to make a short comment about patients with disseminated lupus erythematosis. In that group of patients, we prefer prednisone and we find that the high anti-inflammatory potency makes it a very satisfactory drug. We do not use antibiotics prophylactically in patients on long-term therapy. We treat the acute infections as they appear.

Dr. Smith: We have considered the diet in terms of sodium intake. What about the level of protein and total calories? Would you comment on that, Dr. Mellinger?

Dr. Mellinger: Inasmuch as the therapeutically effective corticoids are essentially catabolic agents, one can routinely expect that there will be nitrogen loss through protein breakdown which can be protected against to some degree by a high protein diet. This should be prescribed just as routinely as a restricted salt diet.

Dr. Keyes: On a strict 1 gram salt diet, it is difficult to maintain a very high protein intake because the higher the protein intake in the diet, particularly in meat, the higher the sodium content.

Dr. Smith: High protein intake seems to be a more reasonable program with prednisone and prednisolone therapy. That is, one can hold the protein intake at a good level with no added salt, and calories roughly in keeping with the total activity and basal metabolic needs.

Briefly, Dr. Mellinger, what about thyroid and testosterone as supplementary measures? We heard quite a bit about this initially and yet it seems to have quieted down recently. Are you still using thyroid as a supplementary measure?

Dr. Mellinger: I treat very few patients with large doses of the adrenal steroids. Most of our patients with endocrine disorders are receiving replacement amounts. There probably is such a thing as corticogenic hypothyroidism and a patient who is receiving the compounds for many months or years may well be benefited by 30 to 60 mg. of thyroid daily. Certainly where it is tolerated and not otherwise contraindicated, supplemental testosterone can be prescribed for the same reasons we discussed under the high protein diet. Many of the patients who have had long-term steroid therapy we see in consultation because of such complications as osteoporosis and other wasting disorders. These can be avoided almost completely if testosterone supplements and a high protein diet are maintained. One hundred mg. of a long-acting testosterone preparation intramuscularly every 2 to 4 weeks is recommended, particularly for a female or elderly patient receiving steroid therapy. For a vigorous young male, perhaps this is not justified.

Dr. Smith: I do not wish to differ much with my associate but suggest that instead of avoiding the protein-wasting effects we would probably delay or minimize them. It is doubtful whether we can reverse the catabolic or wasting properties of the adrenal steroids when they are used in the usual therapeutic doses.

We have now exhausted the time allotted to the panel for formal questions and in closing we would all like to hear from Dr. Mellinger a little more about what Dr. Shaffer was saying in respect to the use of the intravenous preparations of the steroids. Occasions come up in our hospital practice where the patient goes into "shock." We often do not know what the reason is and wonder whether we should use steroids for the hypotensive state. We may see a patient with adrenal insufficiency and some of the questions are: "What steroid should I use?" "Should I go the intramuscular route or the intravenous route? If so, what preparations are available?"

Dr. Mellinger: Of course, any patient in shock should receive his medication intravenously or he probably will not get it. The hospital now has two preparations available for intravenous steroid therapy. There is free hydrocortisone, 100 mg. in alcohol solution, which can be given I.V. in glucose or saline over several hours. There is also available hydrocortisone hemisuccinate which can be given directly and intravenously by syringe. The effect of these compounds is relatively evanescent so that the preparation has to be covered by depo-therapy such as intramuscular cortisone acetate. Hydrocortisone is probably never detrimental to anybody in shock. As a matter of fact, if it is not strictly indicated because of no adrenal insufficiency, it may be indicated because it potentiates the action of pressor agents such as norepinephrine. A combination of these drugs in postoperative or other types of vascular shock is well recognized, acceptable therapy.

Dr. Smith: The program is now open for questions from the floor.

Dr. Haubrich: I have one comment and one question. I will comment very briefly in regard to the "buffered" agents. It is my feeling that the introduction of the "buffered" compounds constitutes primarily an admission of guilt and does not appreciably protect the patient. Conceivably, it might protect a very small fraction of individuals who have never had any experience with ulcer disease. In an individual, however, who has a past history of ulcer disease, it is doubtful that the "buffering," as constituted in these tablets, alters appreciably the ulcerogenic potential of these steroid preparations. Therefore, the patient must be put on a definite program in that regard.

My question is this. In the early years of the corticosteroid age, so to speak, we were given a choice usually between ACTH and cortisone. At that time I was inclined, in most instances, to use ACTH because I had an idea that this was a more physiological approach. With the introduction of these newer compounds, we are hearing less and less about ACTH. I would like to ask the panel what the preference is in regard to ACTH as opposed to these newer steroids.

Dr. Smith: I certainly agree with you. We would all like to maintain a near physiological status for the patient during adrenal steroid therapy. We of the Endocrine Clinic were the last in submitting to prednisone and prednisolone, indeed, to the parent steroids, as preferable to corticotropin. We felt that some of the other steroids of the adrenal, such as the so-called adrenal androgens and estrogens, might have a favorable or buffering effect on the patient at the same time as we were getting a

pharmacological effect from the released hydrocortisone. That concept is hard to prove and is still tenuous. The difficulty with ACTH is in the practical aspects of therapy, such as with the patient who has to self-administer the drug or with the frequency one had to give it in the office. Occasional refractoriness to the ACTH occurs even with the best of preparations. Then, what seems to be a most troublesome problem is trying to standardize a unit ACTH given versus the unit response of the patients. One patient may respond by x milligrams of hydrocortisone output and the next person by 2 x. Even though we are giving 40 units to each we are not getting the same pharmacological effect. Finally, as to sodium retention, and there is no question about it, we run into more difficulty with edema and hypertension with ACTH than we do with prednisone. It looks as though we are giving up the ghost. However, ACTH still has a role, as Dr. Mellinger pointed out, in recovering adrenal cortical function. Dr. Ensign, do you want to add to that?

Dr. Ensign: No, I think that in our long-term therapies it is the practical part which is the most important one. To add just a little to what Dr. Haubrich said about the "buffering" of the steroid preparations, I certainly agree with him that it is an admission of guilt. However, the buffer provided is not enough. We have had some very interesting experiences with patients who have developed ulcers while on therapy with the newer steroids. These have been healed by proper management with the aid of our Gastrointestinal Division. The routine use of large doses of buffering material and protective diets are going to be very important for most patients on long-term steroid therapy.

Dr. Dumke: After seeing how many patients are given cortisone therapy, I am wondering whether significant adrenal suppression goes hand in hand with this therapy? Should I routinely, as many anestesiologists are doing today, administer cortisone preoperatively as we administer atropine or scopolamine? Is there any way in which I can tell whether the patient so treated has adrenal insufficiency? Do you tell the patient he is getting cortisone so that when I see him preoperatively he will be able to tell me? I know you protect him fairly well for elective procedures but we also handle emergency procedures. Quite often the medical record is voluminous and it is difficult to find out just what the patient is getting. Is there any harm in giving 200 mg. of cortisone the night before and then administering an intramuscular dose in the morning at surgery to meet the stress that we produce?

Dr. Smith: Certainly, if there is the slighest indication from the history of any steroid being used recently, I would recommend intramuscular cortisone as you suggested.

Dr. Mellinger: I certainly agree but doubt that you need to give it the night before. The morning of surgery is time enough to give steroid support. In line with the other comment, we actually have cards to give our patients on long-term steroid therapy to carry in their wallets. These cards indicate that the patient is receiving steroid medication, just as the diabetic patient carries a card which says that he requires insulin. It is very important for each patient to be instructed that in event of emergency he must take additional steroid medication. His doctor and family should know it. We do provide that information for the patient to carry on his person.

Dr. Coates: Dr. Monto, you seem to feel quite strongly that cortisone is preferable. Do you feel there is any special attribute of cortisone in hematological disorders, or malignant diseases in general, which the other compounds do not have?

Dr. Monto: I doubt if anyone is aware of the mode of action of the steroids. In hematology we are no exception. All I know is that our results speak for themselves.

Dr. Brush: I have now done six gastric resections with vagotomies on patients who have been on long-term cortisone therapy. After the operation they can be continued on steroid preparations as needed and I would like to point out that the Department of Surgery is available for these operations.

Dr. Smith: We will certainly keep that in mind, Dr. Brush.

Dr. Miller: A question to Dr. Mellinger. There has been some talk about the pituitary being suppressed, i.e., the output of endogenous ACTH being suppressed, as a factor in the unresponsiveness of the adrenal after steroid therapy. Of course, ACTH would not affect this. I would like your opinion.

Dr. Mellinger: Essentially, all the adrenal suppression is indirect and through the pituitary. There is no evidence that cortisone affects the adrenal gland *per se* except through the pituitary. Does that answer the question?

Dr. Miller: Not quite. I mean, is there evidence that the production of endogenous ACTH does not come back promptly after the adrenal steroids are discontinued?

Dr. Mellinger: There is some evidence that it does not come about promptly due to changes in the pituitary or the hypothalamus but the adrenal response is also not prompt. For the latter reason we administer large amounts of exogenous ACTH and begin it before the steroids are discontinued. We certainly cannot stimulate the pituitary, however, by any of these means.

Dr. Smith: With these comments the morning activities are completed.

ELECTRON MICROGRAPHS OF A CYSTINE UROLITH†

JOHN H. L. WATSON*

These first electron micrographs[1] to be taken of kidney calculi illustrate a method for studying the structure of uroliths and other body concretions by the electron microscopy of carbon replicas[2]. They show in cystine calculi in particular that, where the stones are opaque to x-rays and hard, these properties are due to efficient packing of the microscopic cystine tablets into the macroscopic stone. The series shows the cystine crystalline layers at a variety of inclinations to the observer. There did not seem to be any overt changes in morphology from location to location in this stone nor was any core structure determined as such. There were very few granular areas. There was no visible evidence of colloid, the stone being a product of true crystallization from solution. In stones of other genesis it might be that colloidal structures would be demonstrable.

To prepare the carbon replicas the stone was split and the split surface polished and etched in KOH. A carbon film was evaporated upon it from an arc in a vacuum. The film was removed by immersing the caculus in a solution of KOH and mounted from the surface of this solution upon a usual electron microscope specimen screen. These films are carbon replicas which faithfully record the structures of the surfaces upon which they were originally deposited.

The micrographs are positives and wherever the image is lighter in density the carbon film is thinner. The replicas give an illusion of three dimensions which may be exploited in stereoscopy of them. The sloping areas present effectively thicker targets to electrons and are darker in the micrographs, the flat planes are lighter in intensity. The very light areas are regions where the carbon has been effectively 'shadowed' by the structures. The black areas represent deep, abrupt holes or slopes.

REFERENCES

1. Watson, J. H. L.: Electron microscopy of a cystine urolith, J. Urol. 75:940, 1956.

2. Bradley, D. E.: High-resolution evaporated-carbon replica technique for the electron microscope, J. Inst. Metals 83:35, 1954-55.

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† Three of these micrographs were accepted for exhibition at the 26th Annual Meeting of the Biological Photographic Association, Inc. and one of them, Figure 8, won a ribbon in the Photomicrography Class.

The length of the line in the lower right hand corner of each figure indicates one micron at the print magnification. One micron = 0.0001 cms.

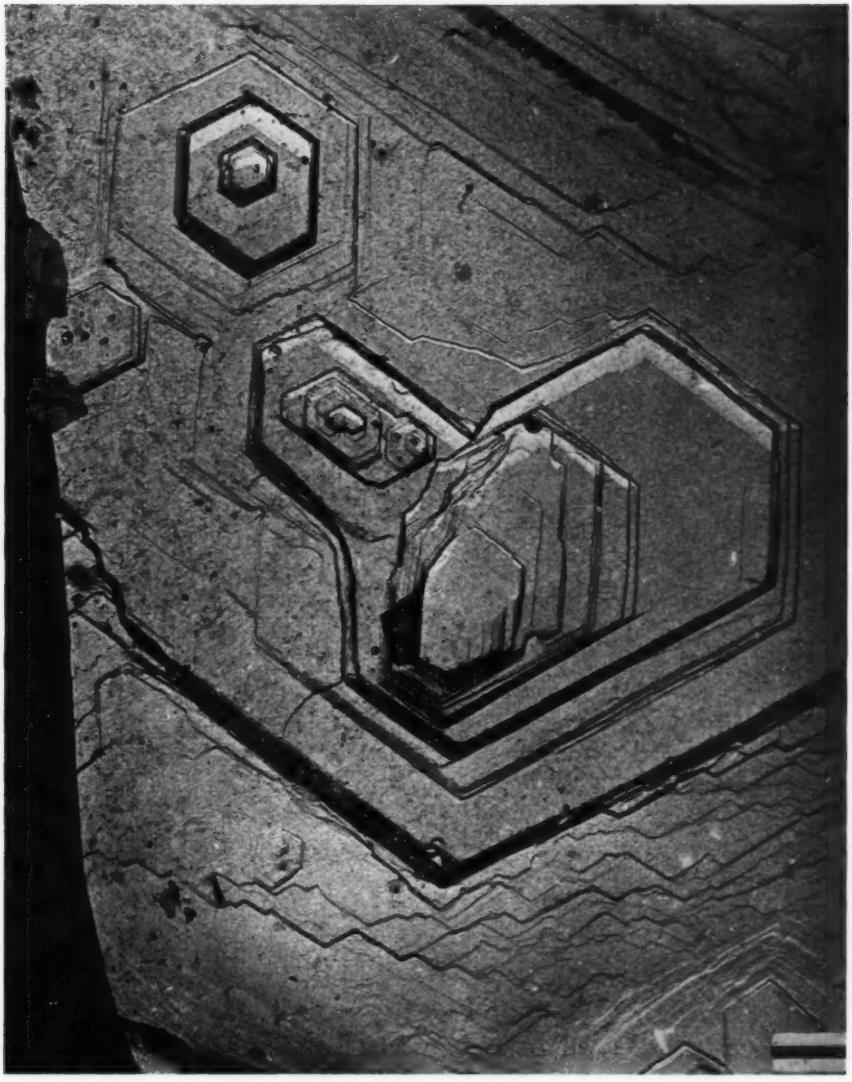

Figure 1

A carbon replica of a cystine urolith x12,000. l-cystine has an hexagonal trapezohedral structure with crystals occurring as tablets with perfect basal cleavage along the (0001) planes This micrograph illustrates this cleavage and shows piles of hexagonal tablets.

Figure 2

A carbon replica parallel to the (0001) planes of a cystine urolith, x12,000. The homogeneity and close packing of the structures are illusrtated.

Figure 3

A carbon replica parallel to the (0001) planes of a cystine urolith, x12,000. Hexagonal depressions and piles of hexagonal platelets are seen, several 'grain boundaries' are observed.

Figure 4

A carbon replica of the split surface of a cystine urolith oriented at an angle of about 75 degrees to the observer so that the (0001) planes are still predominated in the field. The lines of cleavage in the crystal are shown, x12,000.

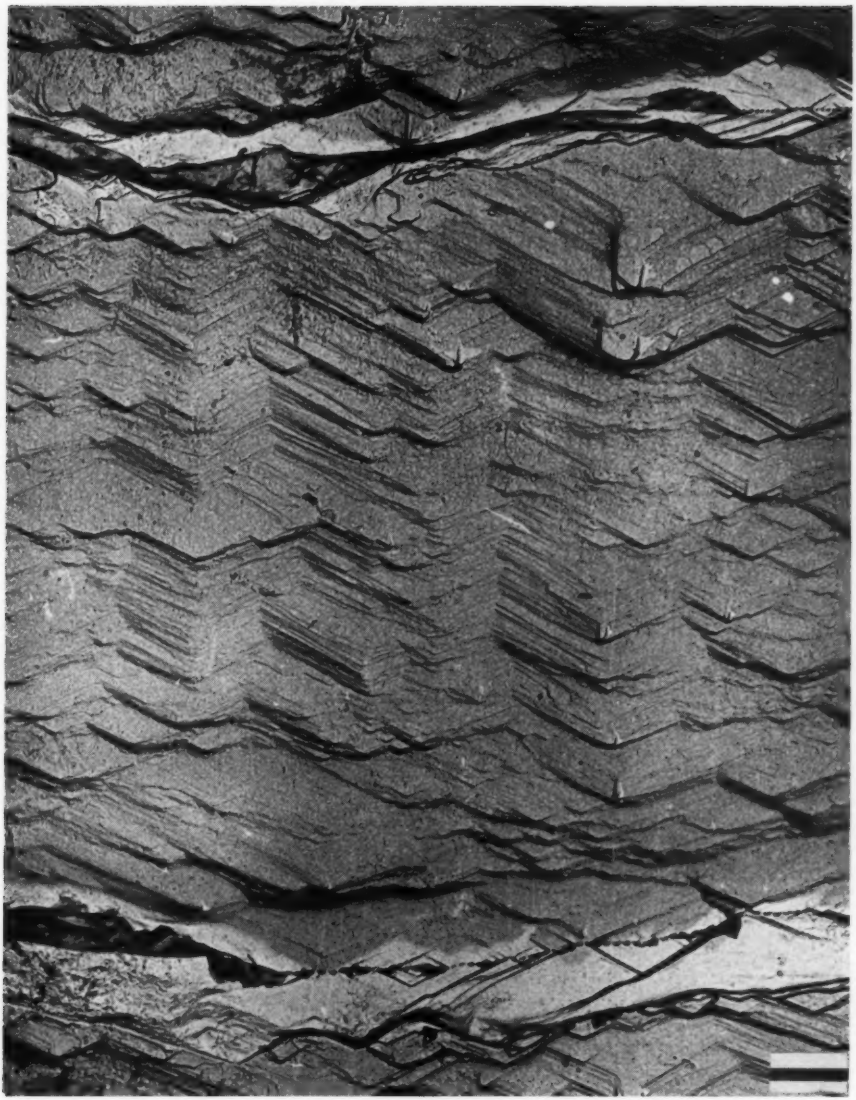

Figure 5

A carbon replica of the split surface of a cystine urolith with the layers tilted so that the edges of the (0001) planes rather than their surfaces are becoming predominant, x12,000.

Figure 6

A carbon replica of the split surface of a cystine urolith where the tablets are at an angle of about 15 degrees to the observer. The tips of the tablets have been etched or broken to protrude so far that they throw long shadows (light triangles), x12,000. Some structure is observable perpendicular to the (0001) planes.

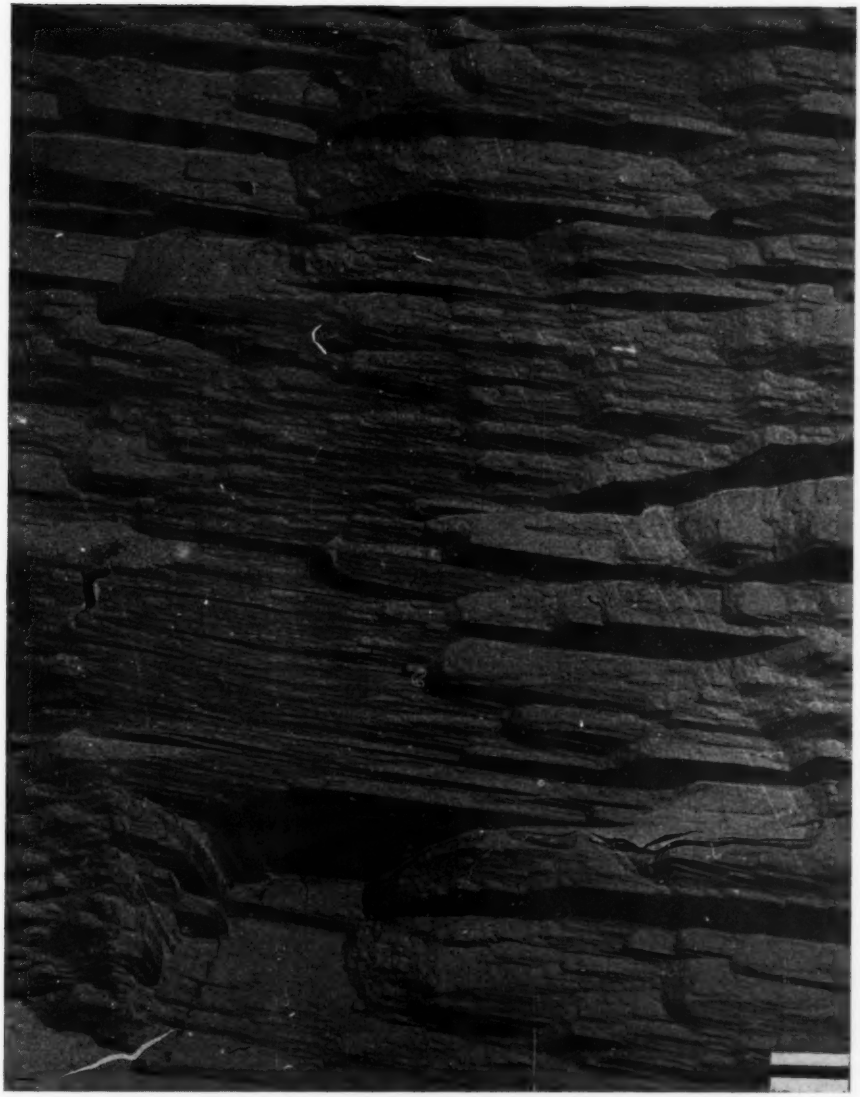

Figure 7

A carbon replica of a cystine urolith split at an angle of about 15 degrees to the observer, to show compact tablet nature of the crystal, x12,000.

Figure 8

A carbon replica of a cystine urolith, observed perpendicularly to the (0001) planes to show the edges of these planes, x12,000. Some structure is visible at right angles to these planes.

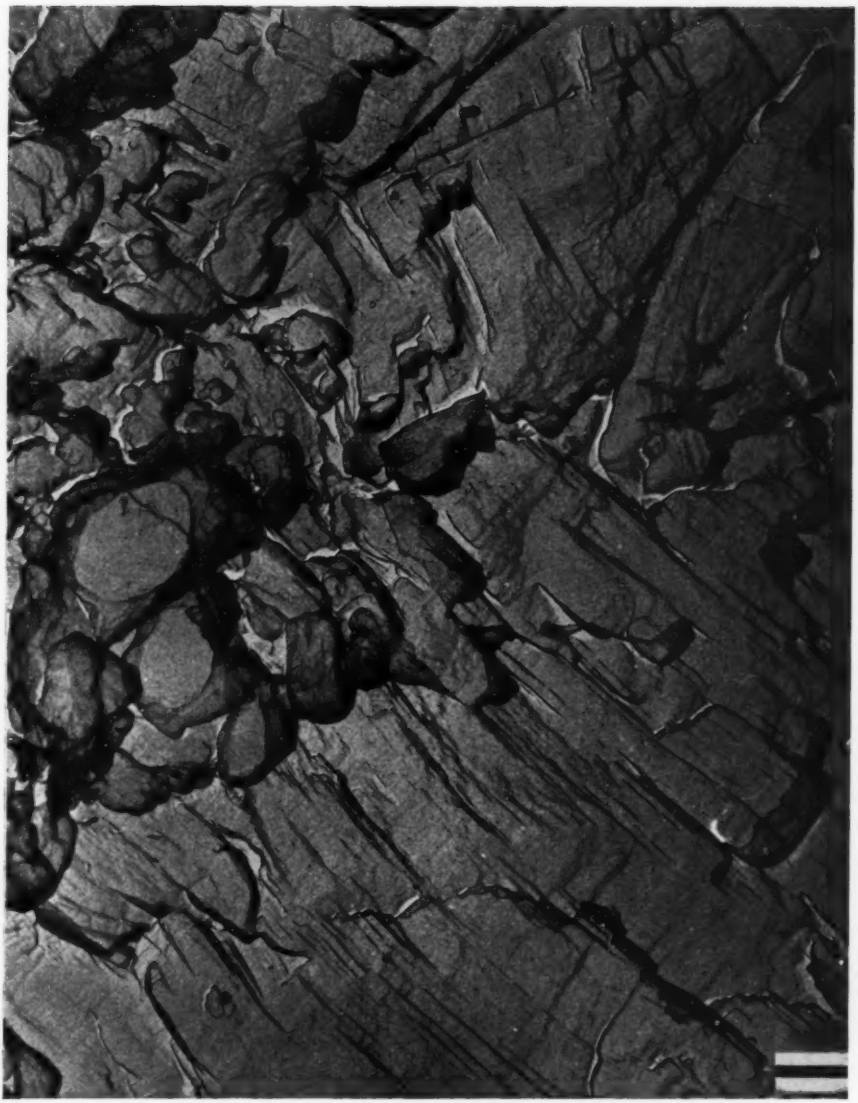

Figure 9

A carbon replica of a cystine urolith to show one of the few areas in which granular material and tiny crystals were seen oriented at random, x12,000.

RETICULOENDOTHELIOSIS

Eosinophilic Granuloma; Non-Lipoid Reticuloendotheliosis (Letterer-Siwe Disease); Lipoid Histiocytosis of Cholesteral Type (Hand-Schuller-Christian Disease)

BRENTON M. HAMIL, M.D.*

The terminology for this condition has been in continuous confusion since the first published material by Hand in 1893. Cases are reported from the literature which are said to fit this classification as far back as 1836.

The earliest reports dealt with a triad of symptoms. Hand[1] described the triad of diabetes insipidus, exophthalmos and membranous lesions of bone occurring in a case diagnosed as tuberculosis. Schüller[2] reported two cases in 1916 with this triad, and Christian[3] reported one case in 1919. Thompson, Keegan and Dunn[4] reported a complete autopsy of a case with the triad of symptoms described by Hand, Schüller and Christian, and the conclusion was drawn that the lesions demonstrated caused the symptoms by the physical mechanics of their location. Denzer[5] in 1926 also supported this thesis. Since this time the anonym Hand-Schüller-Christian Disease is used.

Rowland[6] in 1928 based a treatise on the assumption that the so-called "foam cells", which were considered by pathologists as essential in pathological material to show reticuloendothelial involvement in the pathologic lesions in this disease, were the result of overloading because of a primary disturbance of lipoid metabolism and was similar to the other described storage diseases. This analogy is summarized in Table I[7]. The attention was thus focused upon lipoid fractions, and in 1930 Epstein and

XANTHOMATOSES OR LIPOIDOSES—DISEASES DUE TO DISTURBANCES IN LIPOID METABOLISM.—(Rowland) (Pick).

Name.	Type of lipoid	Blood findings.	Eye grounds.	Spleen, liver glands.	Age.	Bones.	Pathognomonic features.	Skin.	Treatment.	Remarks.
A. Gaucher's disease (20–100 cases)	Cerebroid (kerasin-A sphingo-galactid)	1. Hypochromic anemia 2. Leukopenia 3. Thrombopenia 4. Later, hemorrhagic diathesis	Negative	Spleen markedly enlarged Liver enlarged Slight or no lymph-adenopathy	Infancy to adult life	Mottling and rarefaction with cortical thinning, fusiform appearance ends of femora	1. X-ray appearance of long bones, especially femora 2. Splenic puncture 3. Bone-marrow examination	Subictoric pigmentation of exposed parts in 45%. Yellow thickened pinguecula in eyes in 15%	Splenectomy (fatal in 20%) or radiation (both palliative)	Common in Jews.
B. Niemann-Pick's disease or lipoid histiocytosis (Bloom)	Phosphatids	1. Moderate secondary anemia 2. Slight leukocytosis 3. Vacuolation of non-granulated cells 4. Excess of lipoids in blood	Cherry-red spot in macula lutea occasionally found	Spleen and liver very large Moderate lymphadenopathy	Infancy	Any bones or organs may be invaded by the foam cells	Splenic puncture	Brownish-yellow discoloration	No treatment, all fatal	Mental retardation may be present resembling Tay-Sachs' disease. Most common in Jews.
C. Hand-Schüller-Christian disease (40–50 cases)	Cholesterol and its esters	There may be a hypercholesteremia	Negative	Not enlarged	Any age	Membranous bones involved	1. Defects in membranous bones 2. Diabetes insipidus 3. Exophthalmos 4. Gingivitis and stomatitis 5. Adiposogenital dystrophy	Negative	X-ray treatment of involved area causes prompt local healing but does not stop the progress of the disease.	
D. Tay-Sachs' disease or amaurotic familial idiocy	A prelipoid	Negative	Cherry-red spot in macula lutea usually found	Usually negative	Infancy	Not involved	1. Eye grounds 2. Mental retardation 3. Hyperacousis	Negative	All fatal	Brain shows prelipoid deposits in granular layer and about dendrites of the Purkinje cells Most common in Jews.
E. Xanthomatosis of skin, etc.	Cholesterol and its esters	Negative	Negative	Negative	Any age	Any bones may be involved	.....	Xanthomatosis of any part of skin	Excision, if numerous.	

TABLE I

Storage Diseases Thought in 1930 to be Similar[7]

*Associate Physician, Department of Pediatrics

Presented in part before The American Academy of Pediatrics, Michigan Branch, Detroit, 1954, The Detroit Physiological Society, 1955, The American Academy of Pediatrics, Detroit, 1955, and The Central States Dermatological Society, Detroit, 1956.

Lorenz[8] presented some brilliant work showing the specificity of lecithin, cholesterin and neutral fat in these different endothelial storage diseases. Cowie and Magee[9] did some similar work in 1934 and showed the variability in the lipoid fractions according to the tissue site of the lesions studied; that is, dura as compared with periosteum and bone marrow with viscera. Histologically these lesions are said to consist, early in their development, of a mass of lipoid-laden histiocytes known as "foam cells" which make up more or less rubbery masses arising from the dura in the skull lesions or from the periosteum in the long bones. Scattered throughout the bone marrow and viscera are small lesions which are histologically similar to the bone lesions.[10]

Letterer[11] in 1924 described a case of generalized endotheliosis due to proliferation of the reticuloendothelial apparatus and Siwe[12] reported similar findings in 1933. The so-called "foam cell" was not a feature of this pathology. Abt and Denenholz[13] reported a case in 1936 which showed the clinical and pathological features identified by both of the two authors just mentioned and called it Letterer-Siwe Disease. Since that time "Abts Disease" or Letterer-Siwe Disease has been applied to this group which is characterized by more fulminating over-growth of the reticuloendothelial tissue. There are some eosinophiles such as are found in the pathologic lesion of eosinophilia granuloma but with no foam cells which were considered to be diagnostic of Hand-Schüller-Christian Disease. Merritt and Paige[14] in 1933 had reported a case with exophthalmos, diabetes insipidus, characteristic bone lesions, and severe cutaneous involvement such as characterizes Letterer-Siwe Disease. Pathologic changes were found in the bones, dura, infandibulum of the hypophysis, periosteum, orbits, skin, thymus, pleura, lungs, heart, peritoneum, spleen, liver, pancreas, lymph glands and peritoneal adipose tissue. There was extensive hyperplasia of the reticuloendothelial cells in the spleen and lymph glands without any evidence of lipoid storage but in many sites, such as the dura, bones, lungs and thymus there were typical xanthomatous lesions. The corium in the skin contained localized accumulations of large mononuclear cells similar in morphology to the reticuloendothelial cells found in other regions, but in these cutaneous infiltrations few cells contanied fat or lipoid.

It is readily seen that the transition of terminology necessarily had to evolve through the recognition of a symptom complex, the physical aspects of production of the symptoms, then the phases of the lipoid distribution of its characteristic lesions. Most recently interest has been directed toward grouping cells of these conditions which are characterized pathologically by some greater or less degree of inflammatory reaction of the reticuloendothelial system, either as the result of infection or physical trauma, under one general terminology. Cases observed by Green and Farber[15] concerning the nature of "certain benign, destructive, solitary or multiple lesions" in the bones of 10 children whose progress had been followed from 3 to 10 years, led Farber[16] to discuss a comparison of the pathological material obtained from these 10 patients who had solitary or multiple lesions known as solitary eosinophilic granuloma, with the lesions in the skeleton and viscera in Hand-Schüller-Christian Disease. He also compared them with several examples of what has been known as Letterer-Siwe Disease. He stated that a study of the evolution of the bone lesion in Hand-Schüller-Disease led to the conclusion that all of these conditions represent variations in degree, stage of involvement and localization of the same basic disease process. He did not

imply that any one of these three conditions is a primary xanthomatous process or a secondary manifestation of a primary alteration in lipoid metabolism. He did feel definitely and did so state that "eosinophilic or solitary granuloma of bone is not a new or a separate disease entity." Kennedy and co-workers[17,18] in a report of the treatment of 12 children who had extensive involvement with reticuloendotheliosis of Hand-Schüller-Christian type stated that roentgen radiation in multiple small doses proved effective and suggested its use in all cases.* They suggested that the term "reticuloendothelial group" be used to cover the three conditions under dispute as being similar, and to specify the type as a subtitle, that is, Hand-Schüller-Christian Disease, Letterer-Siwe Disease or Eosinophilic Granuloma. Wallgren[20] has suggested the term "systemic reticuloendothelial granulomatosis" for this group of diseases. Epstein and Pinkus[21] proposed the name "reticulogranuloma" for the granulomatous manifestation of reticulosis. Lichtenstein and Jaffe[22,23] who first called attention to and described the eosinophilic granuloma of bone, suggested the term Histiocytosis X[24] to cover this group of three conditions which have seemed to have an inflammatory inciting cause to stimulate the endothelial cells or histiocytes to abundant proliferation, but since he did not know the exact cause, the "X" was added as a qualifying or compromising factor. Table II shows this classification as prepared after Lichtenstein's presentation. Table III presents the standard nomenclature as used at the Henry Ford Hospital for indexing purposes. Some of the other nomenclatures which have been used in the literature to designate one or more of these pathologic conditions are also presented.

Excellent bibliographies have been published in the evolution of the approach to our present attitude toward these pathologic states of the reticuloendothelial tissue at various periods.

Histiocytosis X

Distribution of Lesions	Clinical Expressions	Age Incidence	Treatment	Prognosis
Localized in bone (one, several, or many foci); no discernible visceral involvement	Eosinophilic Granuloma of bone	Infants, Children, and younger adults (Occasionally older adults)	Curettement or X-ray therapy	Cure (although additional skeletal lesions may sometimes appear)
Acute or subacute course	Letterer-Siwe syndrome	Infants and younger children below age of 3 years; occasional younger adults (adult counterpart of L-S syndrome)	As yet nonspecific; Supportive Antibiotics for secondary infections; X-ray therapy for skeletal and cutaneous lesions	Serious, though probably not invariably fatal; in occasional children, disease may become chronic or go into remission
Disseminated				
Subchronic or chronic course	Schuller-Christian syndrome (not necessarily Christian triad)	Children and young adults; occasional older adults.	As for L-S syndrome; also x-ray therapy or B-hy pophamine for diabetes insipidus; x-ray therapy for early pulmonary infiltration; cortisone?	Guarded, especially for children showing active progression and for patients(adults included)with pulmonary fibrosis and/or pituitary involvement.

TABLE II

Reticuloendotheliosis Classified After Lichtenstein

*Kennedy[19] has had in his experience a total of 46 patients; 9 with skull lesions only, 32 with combined skull and other bones involved, and 5 with no lesions observed in the skull; the mortality was slightly over 23 per cent and x-ray therapy is still being used.

Standard Nomenclature	Other Nomenclature
Eosinophilic Granuloma	Generalized Xanthomatosis (Schuller-Christ.)
Nonlipoid Reticuloendotheliosis: (Letterer-Siwe Disease)	Infectious Reticulo-Endotheliosis(Lett-Siwe)
	Dysostosis-hypophysaria
	Hyperplastic Infectious Reticuloendotheliosos
Lipoid Histiocytosis of Cholesterol (Type. (Hand-Schuller-Christ.Dis.)	Granulo-Xanthomatosis
	Systemic Reticuloendothelial Granuloma
	Inflamatory Histiocytosis
	Reticulogranuloma
	Reticuloendothelial Hyperplasia
	Eosinophilic Xanthomatous Granuloma
	Ess.Xanthomatoses of Normal Cholesterolemic t.
	Lipid Granulomatosis
	Lipogranuloma
	Reticuloendotheliosis Maligna
	Histiocytic Granuloma
	Histiocytosis X

TABLE III

Reticuloendotheliosis Listed According to Standard Nomenclature of American Medical Association

Rowland (1928)[6]; Lichty (1934)[10]; Abt and Denenholz (1936)[13] Wallgren (1940)[20]; Green and Farber (1942)[15]; Hodgson, Kennedy and Camp (1951)[18]; Freud (1951)[25]; and recently Lichtenstein (1953)[24]; Christie and co-workers (1954)[26]; and most recently Merman and Dargeon (1955)[27] and Batson, Shapero, Christie and Riley (1955)[28]. All of the reported cases have been accompanied by lengthy discussion of the descriptive pathology as to the gross character of involved organs and the microscopic examination of tissues, with particular emphasis upon the overgrowth of elements of the reticuloendothelial system. Christie and co-workers[26,28] have ably and thoroughly presented such data and give as references to the excellent description of the pathology, the papers of Abt and Denenholz[13]; Foot and Olcott[29]; Wallgren[20]; Mallory[30]; and Schafer[31]. Christie and co-authors agree with the conclusion of other authors "that the large mononuclears seen in disseminated reticuloendotheliosis may in one instance resemble the large phagocytic cells and in another may appear neoplastic." He states that the diagnosis may be suggested by any one of the described lesions in the skin; the lymphoid tissue (lymphnodes, spleen, thymus); bone marrow; infiltration into lungs, liver and kidney periglomerular interstitial tissue. These manifestations were all the result of endothelial proliferation and infiltration. Careful search could not determine an etiological factor but infection was considered to be of "direct or indirect importance." The manifestations were stated to be "fortuitous", depending only upon the "age of the subject" and the chance distribution of lesions, thus accounting for transitional forms. A diagram is presented to show the age distribution of this "spectrum", age 0-15 months for "disseminated reticuloendotheliosis" (Letterer-Siwe Disease), 2-6 years for Hand-Schüller-Christian Disease and over 6 years for eosinophilic granuloma. When this material was presented before the American Pediatric Society[32] among the discussants was Dr. Arthur E. Abt (Baltimore) who mentioned that in the

era of the middle 1930's when he presented his material, reticuloendotheliosis was in the medical spotlight, much as gamma globulin is today. He also mentioned that the term reticuloendotheliosis is derived from the fact that whenever a small or large part of the mesenchyme of the body has been found to react, this will be either in phagocytic or hemopoitic activity.

Dr. Sidney Farber (Boston) also discussed the paper. He suggested that names were given usually at the period of greatest ignorance concerning the nature of a disease. He was in agreement with Dr. Abt, that the word reticuloendotheliosis would serve only to continue what was a useful term 30 years ago and that the lymphocytes, plasma cells and mononuclear cells described in lesions should not be included in the reticuloendothelial system. He mentioned the use of antibiotics, ACTH, cortisone, nitrogen mustard and folic acid antagonists in use in supportive treatment. He called attention to work being done to show no evidence of any single etiologic agent. He stated that if a comparison was to be made it would be with the exudative and proliferative forms of rheumatic fever or with the protean manifestations of tuberculosis, particularly the lesions which are not produced by the tubercle bacilli actually at the site of the lesion. Recent editorials[33,34] show wide support for this opinion but indicate that there is neither uniformity of opinion about the pathogenesis of these conditions or of the possible etiology; in fact, of the descriptive pathology or terminology. There seems still to be a dispute among the pathologists who comprise the tumor nomenclature committee of the American Medical Association as to whether the pathology is essentially neoplastic or inflammatory[35].

MATERIAL

This paper is presented at this time in order to put on record for the first time a report of the cases which have been indexed under this terminology at this clinic and which have shown either pathological, laboratory or strong clinical confirmation of this diagnosis. This, therefore, indicates the approximate occurrence in a series of 850,000 admissions to this clinic and hospital service in all age groups and from a cross section of economic, racial and industrial population, and represents direct voluntary practice as well as some referral cases. Some have come from social agencies in this community as well as from other doctors and have been referred to various members of a staff which at present consists of 137 permanent full time physicians and 216 residents and internes in all specialties. The cases indexed with this diagnosis affirmed by x-ray or biopsy are briefly presented in the following table (Table IV). Those with a diagnosis of solitary eosinophilic granuloma are grouped together; those with a confirmed diagnosis of Hand-Schüller-Christian Disease (lipoid histiocytosis of cholesterol type) are listed together and those with proven diagnosis of Letterer-Siwe Disease (non-lipoid reticuloendotheliosis) are presented together. The earliest records of any cases fitting this classification in general indexing was in January 1942.

All of these cases had a history of inflammation, either trauma or infection, which may have been primary. The histology of these conditions has been adequately dealt with in the references given for the descriptive pathology. Treatment has consisted of various recognized practices consistent with the period of occurrence of the disease. Currettment or roentgen therapy was used for bone lesions. Antibiotics have

Eosinophilic Granuloma;
Hand-Schuller-Christian (Lip. Ret. End. Chol. Type) and Letterer-Siwe (Non. Lip. Ret. End)

Pt. Case No. C & S BIRTH DATE	ONSET SYMPTOMS	X-RAY	BIOPSY	DIAGNOSIS	RESULTS
B.C. 72 06 19 w.m. 6-27-53 Age 1½ years	Con., Ot. Med., Comatose, 2-16-55, Spinal Fl. neg. High Fever. Protracted Convulsions	2-23-55, Skull lesion Rt. Par. 1 cm., Lungs: Virus pneum.	None	Eosino. Granu. (Poss. early H-S-C- dis.)	Last bone survey 4-6-56—Lesion decreased. Roent. Ther. six week. 5-27-55 to 7-1-55 Normal Prog.
D.B. 74 23 15 w.m. 4-11-43 Age 10½ Years	1-25-54, Local excis. tumor, rt. humerus.	1-25-55, rt. humerus. Les. lower end. Eosin. Gran.	1-31-55. Eos. Gran. Humerus	No other bone studies	Return 3-15-55. Progress x-ray shows healing of lesion. 3-26-55, No evidence of lesion.
A.S. 55 53 64 w.f. 3-27-42 Age 6½ years	10-23-48. Bone cyst. lft. mandible, 3 mo. duration.	No skeletal surveys.	Operation Eosinophliia Gran.	Eosinophilia Granuloma	X-ray treatment. Harper Hospital, left mandible 1-7-49.
T.E. 66 50 06 w.m. 4-16-46 Age 5½ years	Swelling and proptosis left eye. Admitted 1-7-52	1-14-52, lesion lft. sup. orb. ridge, 1½ by 1 cms. Lungs: clear.	Operation 2-6-52 Eosinophliia Gran. H-S-C- dis.	Granuloma consistent with H-S-C dis. or Eosin. Gran. Chest neg., Skull negative.	X-ray treatments 2-21-52 to 3-28-52. Healed 8-9-52. Marrow-Lymphocytic Hyperplasia.
G. G. 74 15 86 w. m. 2-14-41 Age 14 years	5-9-55 Pain left side of head for 1 month. Treated for gastric ulcer from 5-9-54. Hit on side of hd. in fight at onset of symp.	5-9-55, decreased density left parietal bone, suggested Eosinophilic gran.	5-18-55, frozen section and imprint from currettments. Eosin. gran.	5-18-55 Eosin. Gran. left parietal bone.	Roentgen treatment weekly 5-31-55 to 6-25-55 and 10-29-55 to 12-10-55. X-ray 8-5-55; 11-15-55; 1-7-56; 2-8-56. Lesion unchanged. Obese and large stature. Complains of indefinite headaches.
T. D. 66 61 26 w. m. 4-10-30 Age 22 years	12-31-51 Pain and tenderness Rt. side of head for about 2 years.	12-31-51 Other bones and Skull negative for other lesions. Eosinophilic gran. Rt. Temp. Bone.	12-2-52 Biopsy from currettments. Eosin. gran.	Eosinophilic granuloma Rt. Temporal Bone.	No return visit recorded.
H. K. 77 57 7 w. m. 4-5-20 Age 33 years	3-17-53 Pain and tenderness left side of head for several months.	3-17-53 Chest norm. Skull Eosinophilic gran. lesion left parietal bone.	3-21-53 Path report of currettments Eosinophilic gran.	Eosinophilic granuloma left parietal bone.	Roentgen therapy weekly, 4-4-53 to 6-6-53. Progress x-ray 7-11-53 healing. Blood smear normal.
M. D. 71 75 9 w. f. 12-16-16 Age 39 years	12-6-54 Pain and tenderness rt. thigh especially at night for several months.	12-6-54 Possible lesion of Eosinophilic gran. middle of shaft of Rt. femur.	1-3-55 Pathology of Eosinophilic gran. from currettments. Sabaceous cyst Rt. shoulder.	Eosinophilic granuloma shaft Rt. femur.	Relief from pain. 4-27-55 x-ray shows progressive healing of E. G. no other lesions.

Eosinophilic Granuloma;
Hand-Schuller-Christian (Lip. Ret. End. Chol. Type) and Letterer-Siwe (Non. Lip. Ret. End)

Pt. Case No. C & S BIRTH DATE	ONSET SYMPTOMS	X-RAY	BIOPSY	DIAGNOSIS	RESULTS
M. M. 31 63 87 w. f. 9-20-17 Age 39 years	12-23-55 Headache. Referred to Neurology. Findings negative except for tenderness left side of skull.	12-27-55 Area of bone destruction left temporal bone suggests Eosinophillic gran.	1-5-56 Pathology exam. from curretments Eosinophilic gran.	Eosinophilic granuloma left temporal bone.	Roentgen therapy weekly 1-17-56 to 4-10-56. X-ray 1-31-56; 3-20-56; 5-1-56. No further growth of lesion.
J. Y. 39 35 57 w. m. 3-31-41 Age 2½ years	Admitted 7-28-43. Diab. Ins. under control with Pit. Po. Severe lung inv. 10-24-47. 3-14-45 Asthma impr. with Tyrol and Vaccine.	6-25-45 Chronic mastoid Rt. Skull x-ray neg. Mastoidectomy, Rt. Ant. parietal lesion, fine nodular infil., lft. supra orb. lesion, lesion left ileum 1-24-54 to 11-5-54.	1-24-47 Eosinophilic gran. Mastoid.	Lipoid Histiocytosis of Choles. type (H-S-C dis.) Asthma. Labyrinthitis. 6-5-56.	X-ray therapy. Rt. Mastoid 2-25-47 to 12-14-54 with decrease of size of lesion 3-14-55. Vaccine, Ped. Mix. for Asthma weekly since 1-22-51 and T.P.N. and other antihistamine periodically since 1952. Last bone survey neg. 6-6-56. Asthma improved. Symptoms labyrinthitis.
D. K. 51 92 07 w. f. 3-8-46 Age 18 months	9-12-47 Rt. mastoiditis mastoidectomy. 5-13-48 Rash and diab. ins. 11-2-48 Proptosis, lft. eye. 10-29-49 Limp, Rt. leg, pain in pelvis. 3-1-54. Age 8½, Precocious pubertal development, virinary Steroid Determined. Also Hickey-Hare (Carter-Higgins) Salt Test. Vac. Smear. Est. Activity.	9-12-47, mastoid, skull clear. 5-13-48, lesion ant. pariental, sella turcica, orb. plate, femurs, pelvis, lungs.	No biopsy.	H-S-C disease. Diab. Ins. Eosinophilic gran. Precocious. Puberty. Norm. 17-Ketost. Vag. smear Estrog. activity (urinary G. T. of Pit. Orig.)	X-ray therapy 5-29-48 to 12-16-48. Complete healing 4-20-51 diab. ins. under control with Pit. Po. Precocious puberty physiological. Ht. and Dev. consist with Herit. Last x-ray survey 6-28-56 Neg. Norm. Prog. Few inf. since. Urin. Gonad. 1-4 Mouse Ut. U Norm vag. sm. Norm Hyd. St. (E & F) 7.0 17-Keto St. 2.7 (Norm) Indicate no adrenal inf.
T. W. 77 96 17 w. m. 5-23-51 Age 3½ years	6 mos. pro. rt. eye; diab. ins. 18 mos. Ad. 2-3-55	Orb. def. 2-7-55, lesion of lft. ileum, Rt. frontal area of skull 3-10-55 reduced 5-26-55.	None	Lip. Histiocytosis of Choles. type. H-S-C dis.	Pit. Po. control of diab. ins. X-ray therapy of bone lesion 2-9-55 to 3-31-55 Proptosis improved. Normal Proc. Antibiotics as needed for acute infection.
W. B. 34 54 98 w. m. 1-26-24 Age 17 years	10-30-41 Diabetes Insipidus, hypothyroid, hypogonadism Pain in Rt. hip. Severe Malnutrition.	1-6-42 Area of rarefraction Rt. acetabulum and Rt. parietal bone 1-12-42	2-3-42 Curretments from skull reported "collagen" No evidence of H-S-C disease.	Hand-Schuller-Christian disease Hip and skull lesions. Diabetes Insipidus..	Roentgen therapy daily right hip 2-16-42 to 2-20-42. X-ray same 3-12-42. Extended to neck of femur 8-17-42; Improved 11-15-42 and 5-26-43. Diabetes Insipidus controlled with Pitressin Tannate in oil. Malnut Improved.

M. McD. 50 67 83 w. m. 9-27-46 Age 7 months	Ad. 4-26-47. Ex. eryth., cursted eruption. 7-30-47, Rt. mastoiditis, 8-27-47 skull lesion, rt. temporal. 9-29-47 Spon. fracture, Rt. humerus.	4-26-47 to 10-21-47 had miliary inf. both lungs, skull neg., Rt. mastoiditis, skull lesion, rt. temporal Spontaneous fracture of rt. numerus, left jaw & left post parietal lesions.	Lymph node and bone marrow 6-7-47. Chronic lymphadenitis. 7-30-47 eosinophilic granuloma. Mastoid.	Extensive miliary infection in lung, skull, xanthomata, rt. mastoid, rt. temporal, left post parietal, left mandible	X-ray treatment 6-27-47 to 12-2-47. Complete autopsy. 12-5-47, age 15 mos. H-S-C disease, infiltration of lungs, mesenteric & mediastinal lymph-nodes, skin, bone marrow of ribs, lumbar vertebrae, skull and spleen. Fibrosis lungs, hypertrophic gingivitis. Probable so called "transitional" type.
U. G. 73 67 04 w. m. 12-7-50 Age 3½ years	Rash, irritability, malnutrition, anemia, difficult resp. seen by Dr. Possible Leukemia.	3-24-54 negative.	3-23-54, Bone marrow Letterer-Siwe's dis. Non-lip. Reticulo-Endotheliosis	Letterer-Siwe's disease. Reticulo-Endo. Patchy Pneumon, Splenomegaly Hepatomegaly	Autopsy 4-9-54. Generalized lymphadenopathy, Nodes: Mesenteric, hilar, periaortic and Lymphoid tissue. Pneumonitis. Letterer-Siwe's dis. non-lip. reticuloendotheliosis.
J. M. 73 54 18 w. m. 6-29-50 Age 3½ years	Rash, wt. loss, difficulty breathing, en. glands, mal. Ad. 11-11-53.	Lungs: Atelectoasis. Left mid-lung. Bones negative.	Bone Marrow, negative Lymph node neg. 1-8-54. Bone marrow, malig. Reticulo-Endo.	12-16-53, Poss. Letterer-Siwe's dis. Skin biopsy, Reticulo-Endo.	X-ray therapy 11-9-53 to 12-14-53. Complete autopsy 1-9-54, Letterer-Siwe's, Non-lip. Reticulo-Endo. (Poss. trans. H-S-C. dis.)
A. P. *44 31 69 w. f. 9-20-42 Age 18 months	3-29-43, age 18 mos. Adentis 3-28-45, age 30 mos. Anemia and resp. difficulty. Hemoglobin 6.5 gr. Wt. 17#.	4-2-45, Bone lesion, left fronto-parietal area. 4/5 infiltration, both lungs.	Lymph node at Children Hosp. Letterer-Siwe dis.	Letterer-Siwe disease.	X-ray treatment, Harper Hosp. prior to 3-29-45. X-ray treatment skull 4-10-45 to 4-23-45, from 8-24-45 to 9-8-45, last visit 8-10-45; 12-28-45. Coroners aut. consist with L.S. dis. (Zuelser Ch. H.)
C. B. 80 30 64 w. f. 4-12-54 Age 16 months	8-26-55. History of rash from age 3 mo. Draining ears from 6 mo. infection, mastoidectomy recurrent high fevers, poor nutrition, poor appetite. Whining and freting and itching all of time. Rash crusted, purpuric at base and generalized. In Hosp. 8-26-55 to 3-3-56; 5-10-56 to 5-18-56 and 6-9-56 to 6-21-56. Hbn 4.2 gms and 5.5 gms whole blood and packed RBCs twice daily.	8-27-55 Chest neg. Small lesion of lessened density in skull. Bilat. mastoiditis no change 9-19-55; 10-27-55; 11-30-55. Large skull lesion frontal bone 1-24-56; 6-19-56. Further progression of lesions in skull and femora skull map-like-cortex of neck of left femur buckling. New areas in pelvis.	8-25-56 & 12-20-56 Bone marrow full cellularity, overall picture that of infection & toxicity. Blood culture Hem. Staph aureus coagulae positive also from ear and skin. Other bact. thought secondary. Biop. lymph node and skin 8-31-55; 12-3-55; 2-20-56. Overgrowth of endothelial cells Letterer-Siwe dis. non-lipoid reticulo endothelosis.	Letterer-Siwe dis. (non-lipoid reticuloendo) Staph. aur. coagulas. pos. bacteremia; hepatomegaly; splenomegaly. bilat. mastoiditis; skull lesions map-like. Bone lesions both femur varus deform. neck of left femur. Bone lesions in pelvis, rt. humerus; left 6th rib. Hemolytic anemia recurrent.	Roentgen therapy to skull and to both hips 5-15-56 to 6-19-56 daily. Staph. aureus resistant to most antibibotics, sensitive to Chloramphenicol and less so to Erythromycin. These have been alternated in treatment. Cortisone, ACTH or metecortin given continusouly to suppress histiocytic overgrowth and help in some way with immue response. Good skin care. At home most of last 6 mo. Two admissions for about 1 week each for blood. Think she will grow out of her disease.

*443169 Dr. Wulff Zuelzer, Children's Hospital of Michigan kindly supplied report of biopsy, lymph gland and tissue taken from coroner's autopsy.

been used liberally and not always specifically. ACTH, cortisone and antifolic acid drugs or nitrogen mustard have been used or their use has been considered in the more serious cases. This table for these cases needs no further elaboration except for two considerations. Those cases which have shown the best response, even to the point of complete recovery, have had attention given to *purposeful* treatment with surgery, x-ray, steroid therapy, antibiotics, antihistamines or vaccines with effort directed toward the use of whole blood or packed cell transfusions and other supportive parenteral therapy as it seemed to be indicated. Vitamin supplements and supportive blood tonics were used when they could be tolerated. An attempt was made toward good dietary and nutritional therapy. No familial occurrence was observed.

Necropsy pathological reports were available from four cases. Three of these cases were diagnosed Letterer-Siwe Disease (non-lipoid reticuloendotheliosis) and one age 15 months was called Hand-Schüller-Christian Disease (lipoid histocytosis). In this case there was extensive bone involvement with spontaneous fracture of the right humerus although there was generalized organ involvement. This represents the "transitional" type[38].

Three cases have not had tissue removed for biopsy. One (#720619) has been observed for 18 months with a diagnosis of eosinophilic granuloma of the skull. The two other cases have shown at some time the Hand-Schüller-Christian triad of symptoms and have had at some time extensive bone involvement. Both have been observed closely and one without symptoms except for the diabetes insipidus, (#393557) for 13 years and (#519207) for 10 years. Both patients are now in early puberty. The other case of Hand-Schüller-Christian Disease (#779617) with the typical triad of symptoms has been treated for about 18 months. The diabetes insipidus is well controlled with a snuff of a selected small amount of posterior pituitary gland powder which is used once or twice daily. This is a preparation made from beef pituitary gland.* We have not experienced the reccurrence of any of the solitary eosinophilic granulomata which have been successfully treated and neither has there been re-currence in other skeletal locations.

The patient with severe Letterer-Siwe Disease (non-lipoid reticuloendotheliosis) (#803064) has been under continuous treatment for one year from age 18 months, having had some degree of her illness from the age of 3 months. She has had continuous treatment with cortisone, hydrocortisone, ACTH or meticorten (Prednisone, Schering) as well as the continuous use of antibiotics during this time. She has had roentgen treatment for her bone lesions and has had the organism which was obtained from her ear pus, skin lesions, urine and blood stream treated with the antibiotics to which it was most sensitive. This is important not because of the organism, since a large variety have been associated with this disease, but because of the possible effect upon the plasma and tissue factors operative in the immune response if the organism is made only static or if its metabolism is reduced and the organism is not

*This preparation now marketed by Armour Laboratories is a posterior pituitary gland powder in 40 milligram capsules together with an insufflator to make more convenient its use as a snuff. The trade number for the capsule is 3080 and that for the insufflator is 3082. Directions for use are given.

killed.* The steroid preparations have been used in sufficient dosage to suppress the histiocytic overgrowth but it also has been reported to have some action toward the function of the immune mechanism. Mutation of microorganisms and types of resistance that develop by gene mutations in the organism have been shown experimentally[37].

Steroids also contribute to a sense of well being, and there is improvement in the appetite of the patient. This patient has spent most of the last 6 months in her home and is clinically improved although there is extensive organ involvement. This case is to be presented with greater detail in another publication as will also be the patient #519207 who has had the triad of symptoms which characterize the group of cases called Hand-Schüller-Christian Disease (lipoid histiocytosis) and has no evidence of tissue involvement or effect from the disease after 10 years of observation from its onset. The patient (#393557) has had symptoms of allergy during much of his 13 years of observation. This symptom and its treatment is interesting to me because of its involvement with the mechanism of immunity and the cross reactions observed with fungi[38]. As his allergies have been treated his Hand-Schüller-Christian Disease has improved.

CONSIDERATIONS

The rationale which governs our thinking in regard to the pathologic cytology or the cytologic histology of these three conditions must be liberal. They all have similarities but at the same time they have profound differences. They all have some cellular elements in different occurrences that are recognized as not being a part of the so-called reticuloendothelial system. Certainly all of these cellular elements must be bathed in plasma for their nutritional and physiologic exchange of ions, hormones and fractionated proteins which have been shown to contribute to the immune response. This may also apply to the presence of plasma and other cells, said not to be a part of the reticuloendothelial response. There is one thing which the clinician and the physiologist and the biological chemist realize: a cell, an organ, and organism, a group of animals or people are subject to constant change. Nothing is static that lives.

The least serious of these conditions, the eosinophilic granulomata are usually solitary, slow growing, easily healed by the effect of roentgen therapy or simple currettment and are characteristically found in older children and adults who have their hormonal physiology adjusted to act as a matter of regular routine. Hand-Schüller-Christian type is most common to the middle age group of children or poorly nourished young adults and the most serious cases are found in those patients who have the onset in the early years of chilhood when their body defenses including all of the elements which participate in such mechanisms, cellular or otherwise, are less patterened in their response. Letterer-Siwe Disease is the most serious and often fulminating, showing its onset in middle or late infancy at a time when the infant has recently liberated itself from its required excess storages of intrauterine life. The same hormonal unloading can be anticipated, as is true in regard to vatamins[39,40] and steroids[48,49] and the effect upon "resistance" will consequently be altered.

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*Klein[36] stated that the blood corticosteroid levels in several babies who died of infection were very high except one who was in vascular collapse. Talbot[36] stated that data would seem to indicate that death from overwhelming infection, or Waterhouse-Friderichsen Syndrome, is not due to adrenocortical insufficiency.

It is logical in the present state of our knowledge, to which the laboratory scientists have brought us, to know that the physiologic and pathologic functions, as at present learned by histochemical methods, is not a matter of arithmetic in the interpretation of mineral and essential amino acids as determined by intake and outgo. Neither is our knowledge yet to the place that the pathologist can look at a stained, fixed section of tissue and tell from the size and number of granules in cytoplasm or nucleus or vacuoles gorged with phosphatids, cholesterol and its esthers or lecithin and tell whether this condition is beneficial or harmful in the enzyme chemistry of the cell.

Changing environments have altered the behavior of bacteria and viruses as well as the mechanism of response of the cell to inflammation from that observed before the introduction of antibiotics and steroids now known[42]. Goodman[24] has presented ultramicroscope photography to show that leucocytes disintegrate in their attempt to digest virulent bacteria. Nonvirulent strains of bacteria succumb to phagocytosis or remain as bacterial remnants in the cells.

The early works of Sabin, Doan and Forkner[43] and Sabin, Doan and Cunningham[44] called attention in their animal experiments to some of the basic facts which are elaborated upon now by the steroid and histochemists. The emphasis to the reticuloendothelial system in the early 1930's as being all important to immunity and disease processes[44,41] was only the ground work for such investigations as are being done with electrophoresis and chromatography by Janeway and others[45,46,47] in the study of gamma globulin and/or its fraction relationship to antibody. Gardner[48,49] Migeon[50] and Ingle[51] in excellent reports of studies of steroids and their fractionation, their synthesis, and their active constituents put a different interpretation upon the factors commonly mentioned in the earlier consideration of "alarm reaction."

These three conditions and also other disease processes involving a response of mesenchymal cells and their relation to the processes of inflammation will find an easier and more logical explanation with improvement of our knowledge in this direction[52,54]. We will then not be so dependent upon the acuteness with which one person sees and describes characteristics as he observes them grossly or under a microscope in the light of what someone else has described or pictured for him. Eosinophilic granuloma, Hand-Schüller-Christian Disease and Letterer-Siwe Disease are all seen as different degrees of a similar reaction to a lack or decrease, allergy or tiredness of a substance necessary for a response that will maintain good tissue function. This seems to be more logical for consideration than a relative comparison of tissue architecture. The names just mentioned seem adequate and are time-seasoned, if the cause of the reaction that results in the pathology observed is considered from these stand points.

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THE WORTH OF SERIAL ELECTROENCEPHALOGRAMS

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Often it is hard to decide with certainty whether a patient with signs of an intracranial lesion has a neoplasm or a disorder of cerebral circulation. Observation of the course of events — the progress or subsidence of symptoms and signs — must be relied upon in practice to clarify this issue. The problem could be resolved sooner in most instances by angiography or pneumoencephalography. Unfortunately, there is some risk of doing harm to the patient attending the performance of these procedures; so they should be used judiciously upon those patients in whom tumor is strongly suspected and when a delay favors the disease. Electroencephalography‡ is a harmless procedure which provides a mode of information concerning cerebral function that is different than those utilized in physical examination or x-ray study, and the test may be performed as often as needed. Although an EEG provides useful information about patients who have a tumor or a CVA, a single one does not supply definitive points enabling one to distinguish tumor from CVA.

Tumors are electrically inert[1], of themselves unable to influence the brain's electrical patterns. But when they interfere with the function of neurones around them, distortions in the electrical activity of the affected neurones[2,3,4,5], cause disturbed electrical fields which are detectable at the scalp surface by EEG. Thus indirectly is the presence and approximate location of a tumor discovered. Similarly, a part of the brain infarcted by occlusion of its blood supply is electrically inert, since the neurones in the affected part are either destoryed or made incapable of electrical activity. But around the infarcted region there may be a zone of injured neurones from which emanate distorted electrical waves[6,7,8,9]. Whether injured by tumor or by interruption of blood supply the neurones react electrically much the same, yielding in either case few or uncertain clues to the identity of the lesion. Time then is the crucial factor which is required to solve this problem. Tumors enlarge and should cause increasingly intense and wide-spread EEG disturbances (Fig. 1), while the disturbances caused by cerebral vascular lesions should subside when repair occurs and collateral blood supply is established (Fig. 2). It is logical to assume that the data obtained from a series of EEGs taken at proper time intervals would help solve the tumor or CVA question. This survey was undertaken to learn how reliably tumors could be distinguished from CVA with EEG data collected on two or more occasions.

METHODS AND MATERIALS

The records of all patients upon whom more than one EEG had been performed in the EEG laboratory of the Henry Ford Hospital since January 1953 were reviewed. The records of those patients proven to have brain tumors by pathologic means

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‡The terms electroencephalogram and electroencephalography are both designated by EEG; and the different forms of disturbances in cerebral function due to localized or generalized insufficiency of cerebral circulation are designated CVA.

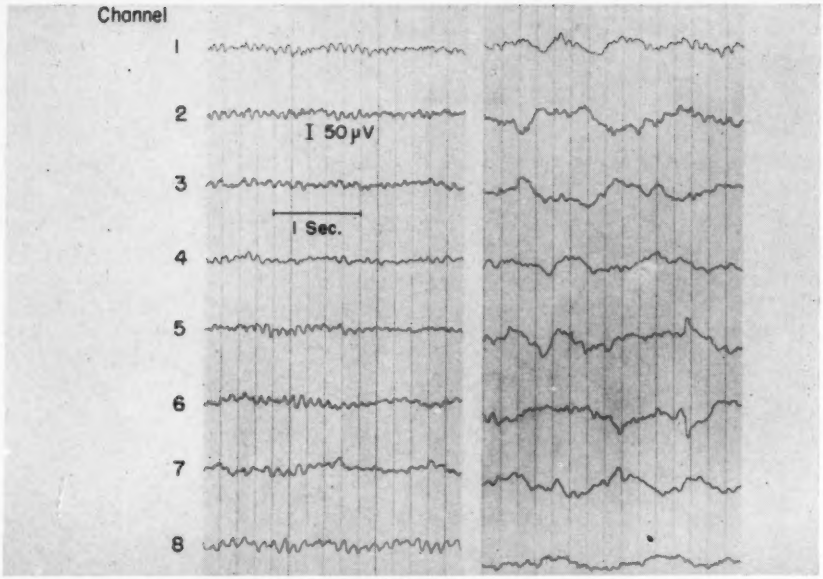

Figure 1

EEG of patient with metastatic tumors. Note the marked increase in slow waves in progress EEG one month after the first. Electrode arrangement is: channel 1 — left frontal to left central, 2 — left central to left temporal, 3 — left temporal to left parietal, 4 — left parietal to left occipital, 5, 6, 7, 8 are right-sided couples in same order as left.

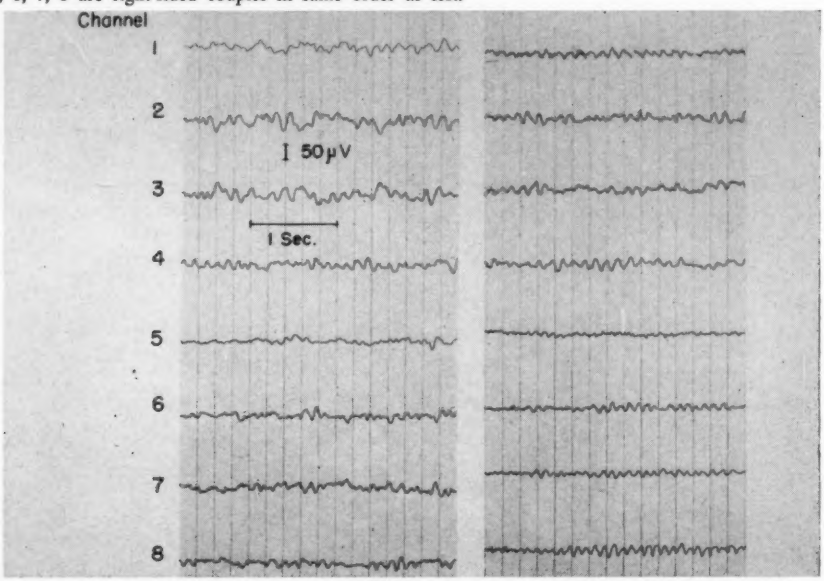

Figure 2

EEG of patient one week after abrupt right hemiplegia. Note loss of rhythmic activity especially on left side which reappears in EEG taken six months later. Note slow waves in left temporal lead sudsiding in later EEG. Electrode arrangement same as in Fig. 1.

(Table I) and records of patients who had CVA proven by pathologic means or confirmed by contrast-media x-ray studies (Table II) were selected for study. Also reviewed were records of patients with CVA that were diagnostically well documented by neurologic evaluation and adequate follow-up (Table III). Case records were not admitted to this study if the nature of the intracranial lesion remained in doubt. Initial EEG tracings were rated normal, borderline, and abnormal; the criteria of normalcy being those generally accepted among electroencephalographers[10,11,12]. EEG patterns are quite variable even in normal persons; so that judgments of EEG records are to some extent matters of opinion.

In this laboratory progress EEGs were considered to be worse than the original or conversely improved by these criteria: If the number per minute of slow waves longer than 2 seconds in duration had increased 10% or more, if the duration of the waves had increased by one-half cycle or more, if the amplitude of the slow waves

Tab. 1 Brain Tumors Verified by Pathology

Case	Tumor Type	First EEG	Progress EEG — Time in Months							
			.5	1	2	4	6	8	12	over 12
1	Meningioma	±		W						
2	Astrocytoma	±		U		B				
3	Astrocytoma	+								W
4	Meiningioma	O	W							
5	Glioblastoma	+	W							
6	Carcinoma	O			W					
7	Carcinoma	+	U							
8	Carcinoma	+	U							
9	Glioblastoma	+		W			W			
10	Carcinoma	±		W	W	W				
11	Astrocytoma	±	W							
12	Astrocytoma	±		W						
13	Glioblastoma	+					U U			
14	Glioblastoma	O					W W			
15	Meningioma	+		W						
16	Glioblastoma	+				W				
17	Glioblastoma	+		W						
18	Carcinoma	+	W							
19	Oligodendroglioma	O							W	
20	Astrocytoma	+								W
21	Meningioma	±								U U W

+ = Positive
± = Borderline
O = Negative

B = Improved
U = Unchanged
W = Worse

Tab. 2
CVA Verified by Contrast X-ray Studies or Pathology

Case	First EEG	Progress EEG — Time in Months							
		.5	1	2	4	6	8	12	Over 12
1	+		U	U		B		B	
2	+		B			B			
3	+				B				
4	+		U						
5	+		B						
6	+	W W		B					B
7	O			W				W	
8	+	B							
9	+			B					
10	+		U						
11	+		U				B		
12	+						B		
13	+	B B							
14	O	W							
15	+	U							
16	+	W							
17	+		NEW	CVA	W				
18	+							W	
19	+		B						
20	+		U	U	B B				
21	+			B					
22	+		B						

had increased 20% or more, or if the source of slow waves at the surface of the scalp had increased. Other points taken into consideration were an increase in the content of 5-7 per second wave activity and an increase of depression and irregularity of the alpha and rapid frequency activities.

RESULTS

The data under consideration have been tabulated in Tables I, II, III. The original EEGs in the group of twenty-one patients with brain tumor were abnormal in eleven patients, borderline in six and negative in four. Eight of the eleven patients with abnormal EEGs developed greater abnormalities in their progress EEGs. The progress EEGs of the other three patients remained unchanged; however, the time between the first and final EEG was only two weeks in two of these patients; hardly enough time to expect a change. Progress EEGs of the patients whose original EEGs were negative or borderline became abnormal except in one borderline case which showed improvement. The tracings in this case being borderline and of dubious

Tab. 3

CVA Diagnosed by Clinical Means

Case	First EEG	Progress EEG — Time in Months							
		.5	1	2	4	6	8	12	Over 12
1	+		U	B		B			
2	+		B			B			
3	+				B				
4	+	W W	B B						
5	+	U			B				
6	+						U		
7	+		B						
8	+					B			
9	+	W							
10	+	B		B				B	
11	+	U							
12	±		B						
13	+	B		B					
14	+					B			
15	+				B				
16	+		B	B					
17	+	B							
18	+							W B	
19	+			U					
20	O		U						
21	+		B						
22	O				U				
23	±			B					
24	+	U U							
25	+		B					B	
26	+			U					
27	+		B						
28	+		W	B		B			
29	+			B					
30	+				U				
31	+	B							
32	+		B						
33	+	W	B						
34	+		U		U				
35	+	B							
36	+		U						
37	+		U			W		B	
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39	+			B					
40	+				B			B	

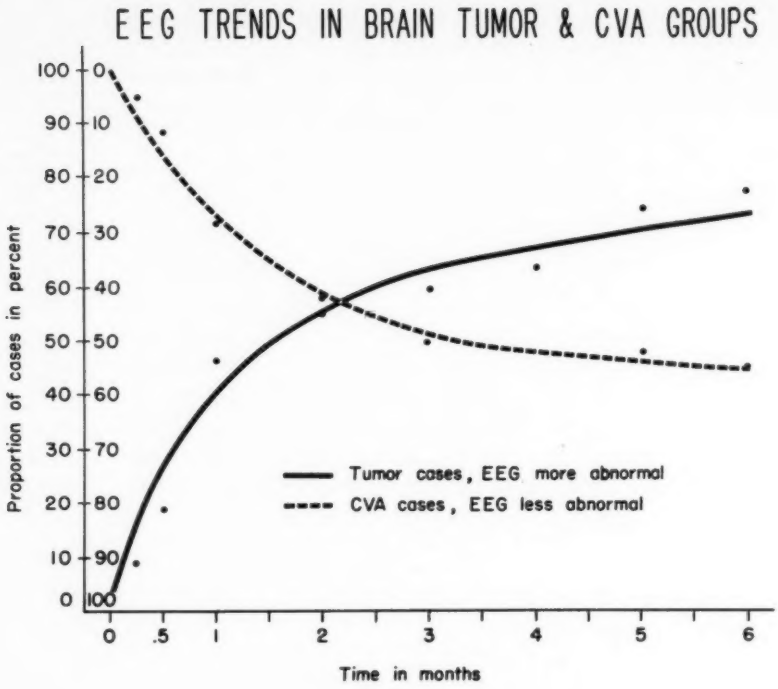

Figure 3

Curves showing when progress EEG's in the tumor group were found worsened and in the CVA group improved. Cases in per cent of total group becoming more or less abnormal for tumor and CVA groups respectively plotted on ordinate. Time after initial EEG that progress EEG was found changed on abscissa. In both tumor and CVA groups more cases changed within the first two months than in equal periods later.

localizing value were difficult to judge; the improvement noted in the final one taken at the fourth month was meagre. By the end of the second month 52% had already established a trend of increasing abnormality in their progress EEGs (Fig. 3). Although an additional 24% of the group worsened, their progress EEGs were not obtained within this period. No EEG was obtained in 9.5% after the one taken in two weeks. Another 9.5% had unchanged progress EEG after six and eleven months respectively. One to three years elapsed in three cases before the EEG was obtained and found to be more abnormal than the original.

All first EEGs of the CVA cases were abnormal except four which were negative and two which were borderline. Of the 62 cases with CVA it was found that 44 (71%) showed improvement, 50% having shown this improvement in their progress EEGs within the first two months. Twenty-one percent remained unchanged but in only four had the progress EEG been obtained after the second month. The EEG became worse in twelve cases (19%), but in six of these after a period of deterioration the EEG improved, thus leaving 10% with final EEGs remaining worse than the first. The increase of abnormality occurred within the first month in seven cases.

DISCUSSION

Most of the patients with brain tumor composing the group under consideration were those in whom the diagnosis was made only after difficult and prolonged study. The original diagnosis of tumor had been tendered in only four of these patients. This group was diagnostically difficult because those patients in whom the diagnosis of tumor was made easily were treated promptly, there being no need and no opportunity for repeated EEG testing. In this group of patients the progress EEGs with one exception became more abnormal. Progress EEGs in the majority (58%) of cases revealed increasingly abnormal trend prior to the end of the second month following the day on which the first EEG had been done. It can be assumed quite safely that had progress EEGs been obtained earlier in all cases, the proportion of the group revealing early EEG trends would have been considerably greater.

One case of improvement of the progress EEG required explanation. It was thought a small hemorrhage had occurred within this tumor just before the first EEG was done, progress EEGs showing apparent improvement while the hemorrhage was being absorbed. Improvement in progress EEGs also might be anticipated in patients with brain tumors when the first EEG had been obtained soon after the occurrence of a convulsive seizure. In addition, transient EEG disturbances caused by certain drugs, metabolic changes, and head trauma, if present when the first EEG was obtained but absent later, could be misinterpreted as an EEG improvement in a patient harboring a brain tumor. However, from the evidence at hand it would appear that such complicating conditions occur infrequently.

Most cases (71%) in the CVA group revealed a trend of decreasing abnormality in their progress EEGs (Fig. 3), but this direction of change was less definite than was the opposite trend in the tumor group. The number improved undoubtedly would have been greater if more progress EEGs had been obtained at least until a time was reached when new CVAs surpassed lesions improving. The proportion of the group (19%) that worsened was fairly large; however, all but 10% finally improved. It was noted that increased abnormality frequently occurred within the first few weeks, later followed by improvement.

The cases that did worsen posed a special problem for they gave the EEG appearances of tumor. Explanations for this transient increased abnormal state were: extension of a thrombus in a vessel, venous congestion, cerebral edema, or circulatory incompetence in a patient first tested in the early promotory period preceding a complete ictus. The few instances when after several months EEGs were more abnormal than the original were best explained by the occurrence of fresh occlusions of other diseased vessels. It is suspected that patients in whom the EEG remained unchanged had lesions which had healed as much as they could before the first test was done.

The patient whose progress EEG is more abnormal than the first should be suspected of having a brain tumor, particularly if the abnormality continues to increase after the first few weeks. On the other hand if the progress EEGs improve, the probability is great that the patient does not have a tumor; a CVA being by far the most likely possibility. The value of progress EEG is enhanced when information derived from them is integrated with clinical data, EEG changes often being explained

clearly by clinical facts and findings. When there is the problem of the patient having a tumor or a CVA it is recommended that a progress EEG be obtained in one month and again in two months. When the situation remains unclarified after two months, progress EEGs should be taken at two to four month intervals.

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International Symposium

HEPATITIS FRONTIERS

October 25, 26, 27, 1956

The professional staff of the Henry Ford Hospital with the initial advice and support of the Board of Trustees and Dr. Robin C. Buerki, Executive Director, of the Henry Ford Hospital, is sponsoring an international symposium on the subject Hepatitis Frontiers. This symposium will be held at the Henry Ford Hospital, October 25, 26, and 27, 1956, in the Clinic Auditorium. The final program follows and has been prepared with the help of the advisory members.

Advisory Members:

Henry L. Bockus	Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania
Charles H. Best	Professor of Physiology, University of Toronto, Toronto, Canada
William S. Tillett	Professor of Medicine, New York University College of Medicine, New York, New York
Gilbert Dalldorf	Director of Laboratories and Research, State of New York Department of Health, Albany, New York
John R. Neefe	Internal Medicine, St. Petersburg, Florida

Local Members
Frank W. Hartman, Chairman
John G. Mateer, Vice-Chairman
Gerald A. LoGrippo, Secretary
James Barron

FINAL PROGRAM

First Morning Session

8:50 A.M. Welcome Remarks
Robin C. Buerki
Moderator: *Charles H. Best,* University of Toronto, Toronto, Canada

9:00 The Structural and Functional Acinar Unit of the Liver: Some Histopathological Considerations
A. M. Rappaport, Associate Professor of Physiology, University of Toronto, Toronto, Canada

9:20 Multiple Parameters Needed to Adequately Describe the Status of the Hepatic Circulation
Ralph W. Brauer, Head, Pharmacology Branch, U. S. Naval Radiological Defense Laboratory, San Francisco, California

9:40 Pathologic Physiology of Hepatitis
Leon Schiff, Professor of Clinical Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio

10:00 Discussion

Jesse L. Bollman, Section on Biochemistry, Mayo Clinic, Rochester, Minnesota

10:20 Intermission

10:40 Geographic Pathology of Hepatitis

Kenneth R. Hill and *G. Bras,* Department of Pathology, University of British West Indies, Jamaica, British West Indies

11:00 Pathologic Anatomy of Hepatitis: Early Stages

Hans F. Smetana, Armed Forces Institute of Pathology, Washington D. C.; University of Delhi, Delhi, India

11:20 Pathological Anatomy of Hepatitis: Late Stages

A. H. Baggenstoss, Section of Pathology, Mayo Clinic, Rochester, Minnesota

11:40 Cirrhosis in Young Females: Its Possible Relation to Hepatitis

Henry G. Kunkel, The Rockefeller Institute for Medical Research, New York, New York

12:00 Discussion

Edward A. Gall, Professor of Pathology, University of Cincinnati College of Medicine, Cincinnati, Ohio

12:30 Luncheon

First Afternoon Session

Moderator: *Gilbert Dalldorf,* State of New York, Department of Health, Albany, New York

1:30 Etiology of Hepatitis

F. O. MacCallum, Virus Reference Laboratory, London, England

1:50 Tissue Culture in the Isolation of the Hepatitis Virus

I. W. McLean, Virus Laboratories, Parke Davis and Company, Detroit, Michigan

2:10 Studies on the Hepatitis Virus

Sven Gard, Department of Virus Research, Karolinska Institute, Stockholm, Sweden

2:30 The Growth of Organized Liver Culture *in vitro* and Their possible Use in the Study of Hepatitis

Frederick B. Bang, Professor of Pathobiology, The Johns Hopkins University School of Public Health; Associate Professor of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland

2:50 Discussion
Thomas H. Weller, Professor of Tropical Public Health, Harvard University Medical School, Boston, Massachusetts

3:10 Intermission

3:30 Epidemiology of Hepatitis
John R. Paul, Professor of Preventive Medicine, Yale University School of Medicine, New Haven, Connecticut

3:50 Epidemiology of Serum Hepatitis
W. Paul Havens, Jr., Department of Medicine, The Jefferson Medical College, Philadelphia, Pennsylvania

4:10 Epidemiology: Military Experience
Ross L. Gauld, Chief, Department of Epidemiology, Walter Reed Army Institute of Research, Washington, D. C.

4:30 Epidemiology: Epidemic in India
Joseph L. Melnick, Yale University School of Medicine, Section of Preventive Medicine, New Haven, Connecticut

4:50 Endemic Viral Hepatitis in an Institution: Epidemiology and Control
Robert Ward and *Saul Krugman,* Department of Pediatrics, New York University College of Medicine, New York, New York

5:10 Discussion
Hans F. Smetana, Armed Forces Institute of Pathology, Washington, D. C.; University of Delhi, Delhi, India

Second Morning Session

Moderator: *John R. Neefe,* St. Petersburg, Florida

Prevention of Hepatitis

9:00 Nutrition as a Protective and Therapeutic Factor in Hepatitis
Paul Gyorgy, Professor of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

9:20 Turbidity Reaction Mechanisms and Turbidity Measurements in the Study of Hepatitis
John G. Reinhold, Pepper Laboratory, University of Pennsylvania, Philadelphia, Pennsylvania

9:40 Selection of Blood Donors
Value of Hepatic Tests for the Detection
Carriers of Viral Hepatitis in the Selection of Blood Donors
Robert F. Norris, Director, Pepper Laboratory, University of Pennsylvania, Philadelphia, Pennsylvania

10:00 General Discussion

10:20 Intermission

11:00 Storage of Blood Plasma
Prevention of Virus Hepatitis by Room Temperature Storage of Pooled Plasma
Garrett Allen, Professor of Surgery, University of Chicago, The School of Medicine, Chicago, Illinois

11:20 Evaluation of the Risk of Transmitting Hepatitis by the Administration of Dried Fibrinogen (Human)
H. D. Anderson, Associate Director, Michigan Department of Health Laboratories, Lansing, Michigan

11:40 The Red Cross Method of Screening Donors, Preparing Apparatus and Protecting Blood Bank Workers
Sam T. Gibson, Associate Director of Blood Program, American Red Cross, Washington, D. C.

12:00 Discussion

Joseph Stokes, Jr., Professor of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

12:20 Luncheon

Second Afternoon Session

Moderator: *William S. Tillett,* New York University College of Medicine, New York, New York
Prevention of Hepatitis: Chemical and Physical Agents

2:00 Ultraviolet Radiation
Joseph Stokes, Jr., Professor of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

2:20 Ionized Radiation
John G. Trump, Professor of Electrical Engineering, Massachusetts Institute of Technology, Boston, Massachusetts

2:40 Gamma Radiation — Cobalt^{60}
Russel T. Jordon, City of Hope Medical Center, Duarte, California
Lloyd N. Kempe, University of Michigan Medical School, Ann Arbor, Michigan

3:00 Combined Effect of Thermal and Ionizing Radiation
Ernest C. Pollard, The Josiah Willard Gibbs Research Laboratories, Yale University, New Haven, Connecticut

3:20 General Discussion

3:40 Intermission

4:00 Chemical Sterilization: Beta-Propiolactone

Gerald A. LoGrippo, Division of Microbiology, Department of Laboratories, Henry Ford Hospital, Detroit, Michigan

4:20 The Toxicology of Beta-Propiolactone

Annetta R. Kelly, Division of Pharmacology, Department of Laboratories, Henry Ford Hospital, Detroit, Michigan

4:40 Combined Ultraviolet Radiation and Beta-Propiolactone

Frank W. Hartman, Consultant, Department of Laboratories, Henry Ford Hospital, Detroit, Michigan

5:00 Discussion

Gilbert Dalldorf, Director of Laboratories and Research, State of New York Department of Health, Albany, New York

6:30 Dinner

Third Morning Session

Moderator: *Henry L. Bockus,* Graduate School of Medicine, University Pennsylvania, Philadelphia, Pennsylvania

Differential Diagnosis: Laboratory Methods

9:00 Tentative Classification of Some Current Types of Liver Injury on the Basis of Electrophoretic Serum Analysis

G. Viollier, Basle, Switzerland

9:20 The Use of Flocculation Tests in the Differential Diagnosis of Hepatitis

N. F. MacLagan, Professor, Department of Chemical Pathology, University of London, London, England

9:40 The Serum Glutamic Oxalacetic Aminopherase (Transaminase) as a Diagnostic Test in Hepatitis

Felix Wroblewski, Sloan-Kettering Institute and Memorial Hospital, New York, New York

10:00 Bile Pigments of Serum in Disease of the Liver

Jesse L. Bollman, Section of Biochemistry, Mayo Clinic, Rochester, Minnesota

10:20 The Diagnosis of Hepatitis by Needle Biopsy

Edward A. Gall, Professor of Pathology, University of Cincinnati College of Medicine, Cincinnati, Ohio

10:40 Discussion

Hector Ducci, Santiago, Chile, South America

11:00-12:30 Round Table: Differential Diagnosis: Clinical

Sheila Sherlock, Department of Medicine, University of London, London, England
Robert R. Linton, Surgeon, Boston, Massachusetts
Charles S. Davidson, Associate Professor of Medicine, Harvard Medical School, Boston, Massachusetts
Victor M. Sborov, Internal Medicine, Redwood City, California
Leon Schiff, Professor of Clinical Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio
G. A. Martini, Hamburg, Germany

Third Afternoon Session

Moderator: *Cecil Watson,* University of Minnesota Medical School, Minneapolis, Minnesota

1:30 Management of Hepatitis

Roderick Murray, Director, Division of Biological Standards, National Institutes of Health, Bethesda, Maryland

1:50 Management of Coma

Charles S. Davidson, Associate Professor of Medicine, Harvard Medical School, Boston, Massachusetts

2:10 Steroid Therapy in Hepatitis

Hector Ducci, Santiago, Chile, South America

2:30 General Discussion

2:50 Intermission

3:10 Round Table: Course and Prognosis of Hepatitis

Sheila Sherlock, Department of Medicine, University of London, London, England
John R. Neefe, Internal Medicine, St. Petersburg, Florida
Hans Popper, Pathologist, Cook County Hospital, Chicago, Illinois
William S. Tillett, Professor of Medicine, New York University College of Medicine, New York, New York
Henry G. Kunkel, The Rockefeller Institute for Medical Research, New York, New York
M. Bjorneboe, Copenhagen, Denmark

5:00 Adjournment

INTRODUCTION TO NEW STAFF PERSONNEL

JOSE BEBIN, M.D., Ph.D., joined the Division of Neurology and Psychiatry as an Associate in Neuropathology on July 1, 1956. Dr. Bebin is 37 years of age and a native of Peru. He received his B.S. from the University of San Marcos, Peru, and his M.D. from the same school in 1943. He served an internship at the Loyza Hospital, Lima from 1943 to 1944 and a residency in Neurology at the Hospital St. Toribio de Mogrovejo. Graduate training in Neurology and Neuropathology was received at the Hospital Salpetriere, Paris, 1948-1949 and the Instituto Cajal, Madrid, 1949-1950. Dr. Bebin was the Guggenheim Fellow in Neuroanatomy and Neuropathology at the University of Michigan Graduate School, 1950-1951. While at the University he completed work for the M.S. and Ph.D degrees. Since 1952 he has served as a member of the staff of the Neuropsychiatric Institute and Instructor in Neuropathology at the University of Michigan. He is a member of the Washtenaw County Medical Society, American Academy of Neurology and Sigma Xi. He is married and resides at 3311 West Chicago, Detroit.

ROBERT JOHN BLOOR, M.D., joined the Department of Radiology as an Associate in Radiotherapy on July 1, 1956. Dr. Bloor is 40 years of age and a native of Boston. He received his B.S. from the University of Rochester and M.D. from Harvard Medical School, 1941. He served an internship at the University of Chicago Clinics, 1941-1942 and residencies in Radiology at Strong Memorial Hospital, July to September 1942 and July 1946 to June 1947. He was Assistant in the Diagnostic Division, Department of Radiology, Strong Memorial Hospital from July 1947 to December 1949. From January 1950 to June 1956 he was in charge of the Radiotherapeutic and Radioisotope Division, Department of Radiology, Strong Memorial Hospital. He was appointed Instructor in Radiology at the University of Rochester, July 1947 and promoted to the rank of Assistant Professor, July 1950. He is a veteran of World War II and a member of the American Medical Association, the Radiological Society of North America, and the American Radium Society. He is married with three children and resides at 7352 Poe, Detroit.

SHIRLEY A. JOHNSON, Ph.D., joined the staff as a Research Associate in the Department of Laboratories on June 4, 1956. She is 34 years of age and a native of Mervin, Sask., Canada. Dr. Johnson received her A.B. in 1945 and Ph.D. in 1949, both from the University of Toronto. Recently she has been associated with Wayne University carrying out studies in blood coagulation. She is a member of the American Chemical Society, the International Hematology Society and Sigma Xi. Dr. Johnson resides at 4863 Second, Detroit.

WILBUR R. McCRUM, Ph.D., joined the staff as Research Associate in Neurosurgery on February 15, 1956. He is 35 years of age and a native of Whittemore, Michigan. Dr. McCrum received his A.B. from Alma College and M.S. and Ph.D. from the State University of Iowa in 1951. From 1951 to 1955 he served as Instructor in Neuroanatomy at the University of Colorado Medical School. He is a member of the American Association of Anatomists, Sigma Xi and Gamma Alpha Graduate Scientific Fraternity. Dr. McCrum is a veteran of World War II. He resides at 1300 Bethune, Detroit.

CORNELIUS EDWARD McCOLE, M.D., joined the staff as an Associate in Ophthalmology on July 15, 1956. Dr. McCole is 31 years of age and a native of Wilkes-Barre, Pennsylvania. He is a graduate of Princeton University and received his M.D. from the University of Pennsylvania in 1949. Dr. McCole interned at the Robert Packer Hospital, Sayre, Pennsylvania and served a year of residency in Pathology at the same hospital. He served a two year residency in Ophthalmology at Johns Hopkins Hospital followed by two years service in the U. S. Army Medical Corps. From 1955 to 1956 he completed his residency in Ophthalmology at Johns Hopkins Hospital. Dr. McCole resides at 150 West Euclid Street, Detroit.

STEPHEN GRAHAM MAY, M.D., joined the Division of Neurology and Psychiatry as an Associate in Psychiatry on April 23, 1956. Dr. May is a native of New Hampshire and is 33 years of age. He received his B.S. in 1942 from the University of New Hampshire and M.D. from Johns Hopkins Medical School in 1946. He served an internship at the Newton-Wellesley Hospital and residency from 1948-1950 at the Letterman Army Hospital, San Francisco. He was Division Psychiatrist of the 24th Infantry Division in Toyko in 1951 and from 1952 to 1954 Chief of the Closed Psychiatric Section, Brooke Army Hospital, Fort Sam Houston, Texas. Since 1954 he has been Chief of the Psychiatric Service of the Valley Forge Army Hospital, Phoenixville, Pennsylvania. Dr. May is a member of the American Psychiatric Association. He is married with four children and resides at 19981 Doyle Place West, Grosse Pointe Woods.

JOSEPH P. SZOKOLAY, M.D., rejoined the staff as an Associate in Medical Clinic No. 1 on July 15, 1956. Dr. Szokolay is 44 years of age and a native of South Bend, Indiana. He received his A.B. from Indiana University in 1940 and his M.D. from the same University in 1942. Dr. Szokolay served an internship at Henry Ford Hospital, 1942 to 1943 and a residency in Medicine, 1944 to 1948. He was Chief Medical Resident from 1945 to 1948. From 1948 to 1952 he was Associate in the Division of General Medicine and from 1952 to 1953 Physician-in-Charge of the Geriatrics and Physical Medicine Section. In 1954 Dr. Szokolay was in private practice

in South Bend. The following two years he served as Major in the Army Medical Corps, Fort Gordon, Georgia and as Assistant Chief of the Medical Section. Dr. Szokolay is a member of the American Medical Association, and the Henry Ford Hospital Medical Association. He is married with four children and resides at 12028 Kentucky, Detroit.

GEORGE MILTON WILSON, JR., M.D., joined the staff as Associate in the Division of Arthritis on July 1, 1956. He is 31 years of age and a native of Washington, D. C. Dr. Wilson received his pre-medical training at Cornell University and George Washington University and his M.D. from Syracuse University in 1948. He served an internship at the U. S. Navy Hospital, Portsmouth, Virginia, 1948-1949 and a residency in Medicine at the University of Colorado Medical Center, Denver, 1951-1954. While with the University he completed work for the M.S. in Medicine. From 1954 to 1955 he was the National Institutes of Health Clinical Trainee in Arthritis at the University of Colorado Medical Center and served in a similar capacity at the Mayo Clinic, Rochester, Minnesota from 1955 to 1956. Dr. Wilson was Base Medical Officer at the U. S. Navy Subase 128, Pearl Harbor, 1949-1951. He is a member of Nu Sigma Nu, American Rheumatism Association, American Federation for Clinical Research and the American Medical Association. He is married with three children and resides at 934 Nottingham Road, Grosse Pointe.

ABSTRACTS OF RECENT PUBLICATIONS OF THE PROFESSIONAL STAFF OF THE HENRY FORD HOSPITAL AND THE EDSEL B. FORD INSTITUTE FOR MEDICAL DESEARCH

FOOD PUMP: A NEW APPROACH TO TUBE FEEDING. J. BARRON, J. PRENDERGAST, M. W. JOCZ. J. A. M. A. 161:621, 1956

As a result of cooperative effort by the medical and engineering staffs of the Chrysler Corporation and the Henry Ford Hospital a sturdy, dependable food pump has been designed. These pumps have been useful in supplying adequate pressure to force liquified natural foods through small plastic tubes. With these pumps the delivery rate remains constant, regardless of the position of the patient.

TUBE FEEDING WITH NATURAL FOODS IN ELDERLY PATIENTS. J. BARRON AND L. S. FALLIS. J. Am. Geriatric Soc. 4:400, 1956.

The vital reserves of geriatric patients are limited, and as a consequence the nutritional status of the patient is one of the most important factors in determining a favorable outcome of any medical or surgical program of treatment. The restoration and maintenance of nutritional balance in this group of patients is only now beginning to receive the emphasis it deserves. Elderly patients, often with little or no desire to live, present some of the most difficult feeding problems. In these patients, tube feeding with natural foods presents the real advantages of good tolerance, low cost, and greater clinical benefit.

MECHANICAL RESPIRATOR FOR NEWBORN INFANTS AND OTHER PATIENTS. PRELIMINARY REPORT. A. R. BAUER. J. A. M. A. 161:723, 1956.

Artificial respiration in newborn infants is still considered necessary despite its potential risk. Wittenberger reviewed the subject and Day demonstrated the relative safety and efficiency of higher pressures in the lung for shorter periods, supporting the feasibility of such treatment. The delicacy, rapidity, and variability of respiratory movements increase the problem of simulating them mechanically. Also, the rapidly changing chemical factors are difficult to anticipate by a rhythmically cycled respirator. With the above in mind, an apparatus was designed which would deliver a positive pressure into a face mask and simultaneously give a negative pressure in a body cuirass placed over the chest and abdomen. A lever moved by the abdomen will "trigger" each inspiratory action of the apparatus to supplement that of the patient. In case of complete apnea, this is done by an attendant. Oxygen may be fed into the face mask. The pressures are regulated within limits of safety and efficiency. Clinical investigation of this model and a larger one for older patients is planned to determine their value.

TREATMENT OF URINARY TRACT WITH TRIPLE SULFONAMIDES AND A PENICILLIN-TRIPLE SULFONAMIDE MIXTURE. A COMPARATIVE STUDY. A. W. BOHNE AND W. E. CHASE. Am. J. M. Sc. 231:389, 1956.

A clinical and bacteriological study was conducted in 148 out-patients (98% adult females) to compare the effectiveness of two oral preparations, a triple sulfona-

mide mixture and a combination of triple sulfonamides with benzathine penicillin, in uncomplicated acute and chronic infections of the urinary tract. In pre-medication urine specimens, obtained by catheterization, a variety of organisms was found by microscopic examination and culture, with *E. coli* present in 65%. Medication consisted of an initial dose of 2 gm. followed by 0.5 gm. four times a day for seven days, representing one-half or less of the usual dose of sulfonamides. Seven days after termination of medication, each patient received a routine urological examination, including laboratory studies of the urine. There was no significant difference in effectiveness between the triple sulfonamides and the penicillin-sulfonamide combination, 79% of 71 patients having been freed of urinary tract infection by the former and 75% of 77 patients by the latter, with persistence of infection in the remainder. The former eradicated *Proteus vulgaris*. The latter was the more effective in preventing growth of organisms not present in pretreatment cultures. Both preparations were active against coccal infections.

Sensitivity reactions occurred in 2% but subsided promptly on withdrawal of antibacterial medication and use of supportive measures. There was no evidence of crystalluria, gastrointestinal disturbance, or other serious side effects.

TEMPERATURE AND HOST CELL FACTORS IN THE GROWTH OF INFLUENZA VIRUS (PR-8 STRAIN) IN AVIAN TISSUES IN VITRO. J. M. COLVILLE, J. M. DUNBAR AND H. R. MORGAN. J. Immunol. 76:264, 1956.

Tissue culture techniques were employed in an investigation of the capacity of various avian tissues to support the growth of the PR-8 strain of influenza A virus. The variables of environmental temperature, chemical composition of the culture medium, innoculation interval, and age of the tissues were studied for their effects on viral replication. Experimental results indicated that these variables appeared to influence the reproduction of the virus only in so far as they were compatible with the life of the host cells in culture. The resistance or susceptibility of host cells to viral infection appeared to be in part a function of the developmental stage of the host cell and in part a function of the type of host cell. Heart tissue from embryos of various ages or from hatched two day chicks were routinely unable to support viral multiplication while chorio-allantoic membrane from embryos of differing ages consistently supported growth of the virus. Other tissues such as skin, muscle, intestine, liver, and lung demonstrated a changing pattern of susceptibility which varies with the age of the tissue. Multiple tissues from hatched two day chicks routinely failed to support viral growth.

A COMPARATIVE CLINICAL TRIAL OF UROGRAPHIC MEDIA: RENOGRAFIN, HYPAQUE, AND UROKON. W. R. EYLER, D. R. DREW AND A. W. BOHNE. Radiology 66:871, 1956.

The search for a contrast medium for excretory urography, which produces ideal anatomic demonstration and has no hazard to the patient has produced two new preparations, Renografin and Hypaque, both having the same chemical base. This study is based on 900 unselected urograms. The first study consisted of three series of 200 patients each in which the contrast materials, Urokon, Renografin and Hypaque were given and evaluated by physicians who did not know which preparation they

were using. An additional 300 cases were done using Renografin in order to obtain further information about reaction rates, and possibly information about serious reactions. The only serious reaction which occurred in the whole series of 900 patients, followed the injection of Hypaque. The additional 300 cases using Renografin showed a slightly higher reaction rate than the first series. An interesting sidelight was obtained after correlating the ages of the patients with the quality of the pyelogram. The number of excellent quality pyelograms declined sharply at the age of 40 and more sharply after the age of 50. The number of poor pyelograms increases markedly above the age of 60. These figures are valid regardless of the contrast material used.

METASTATIC CANCER OF THE MANDIBLE — AN EDITORIAL. F. A. HENNY. J. Oral Surg. 14:253, 1956.

The increasing incidence of metastatic cancer involving the mandible dictates the need for a greater awareness of this problem and an intelligent survey of modern therapy for its control. The cardinal symptoms are transient discomfort or spontaneous anesthesia of one side of the lower lip. Hormonally dependent tumors may respond to ovariectomy, cortisone therapy or hypophysectomy. Lesions presenting after such therapy may be treated by resection and/or radiation therapy when they are the only evidence of metastatic disease. Resection of the mandible when done must extend above the mandibular foramen and anterior to the mental foramen, since it is safe to assume that the entire contents of the mandibular canal are involved. It is the obligation of the oral surgeon to be aware of the ever present possibility of metastatic disease within the mandible and to cooperate fully in its local control.

PREGNANCY AND CARDIAC OPERATIONS. E. J. IGNA, M. F. DETRICK, C. R. LAM, J. W. KEYES, AND C. P. HODGKINSON. Am. J. Obst. & Gynec. 71:1024, 1956.

Obstetrical rehabilitation by cardiovascular surgery has reopened the question of risk for the pregnant patient with congenital or acquired heart disease. Twenty-two patients subjected to cardiac operations prior to or during pregnancy are reviewed from an obstetrical standpoint. Three patients who had division of patent ductus arteriosus, one during pregnancy, had uneventful term deliveries. The Blalock procedure for tetrology of Fallot was attempted in three patients. In one, the operation was unsuccessful and resulted in two premature deliveries followed by death six month after the second delivery. The second patient had an uneventful term delivery and the third, a spontaneous abortion. Commissurotomies have been performed in sixteen patients. In five patients operated during pregnancy, uneventful gestations and deliveries occurred. In eleven patients operated prior to pregnancy, seven experienced no cardiac degradation during subsequent pregnancy and had four term deliveries, one premature delivery, and two spontaneous abortions, while in the remaining four, two required strict medical regimes throughout pregnancy and two, who had no surgical benefit, were subjected to hysterectomy during the second trimester.

*STUDIES ON SUCCINIC DEHYDROGENASE. I. PREPARATION AND ASSAY OF THE SOLUBLE DEHYDROGENASE. E. B. KEARNEY AND T. P. SINGER. J. Biol. Chem. 219:963, 1956.

Extraction of rat liver or beef heart mitochondrialacetone powder with alkaline TRIS buffer resulted in complete solubilization of succinic dehydrogenase. By means of this technique the enzyme has been extracted from a variety of animal tissues. Soluble succinic dehydrogenase from *P. vulgaris* has been obtained by sonic oscillation. Cytochrome *c* and the dyes conventionally used for the assay of mitochondrial preparations of the dehydrogenase do not react with the soluble dehydrogenase, and ferricyanide is a relatively poor acceptor. Phenazine methosulfate is the acceptor of choice with the solube dehydrogenase. An assay method, based on the use of this dye, has been described. Some of the properties of succinic dehydrogenase from *P. vulgaris* have been examined.

EPIDERMOID CYSTS OF THE BONY PHALANGES. A. P. KELLY, JR. AND R. H. CLIFFORD. Plast. & Reconstruct. Surg. 17:309, 1956.

The authors report four additional epidermoid cysts of the bones of the fingers. There were 27 previous cases reported, none of which had been diagnosed preoperatively. The earlier cases had partial finger to ray amputations because of unfamiliarity with the nature of the lesion. All the authors' cases were preoperatively diagnosed, permitting the retention of the distal phalanx in three cases and a partial distal phalanx amputation in one. The authors' cases were seen over an eighteen month period leading us to believe the lesion is considerably more common than the paucity of reported cases would indicate.

PREOPERATIVE DIAGNOSIS OF SEQUESTRATION OF THE LUNG BY AORTOGRAPHY. L. J. KENNY AND W. R. EYLER. J. A. M. A. 160:1464, 1956.

This is the first published report of the use of aortography for specific preoperative diagnosis in a case of pulmonary sequestration.

EFFECTS OF COCHLEAR LESIONS ON THE THRESHOLD RESPONSES OF THE AUDITORY CORTEX IN CHRONIC EXPERIMENTS. R. S. KIMURA, H. F. SCHUKNECHT AND S. SUTTON. J. Comp. & Physiol. Psychol. 49:96, 1956.

A study was made of the effect of restricted lesions of the cochlea on the threshold of the cortical response in cats. Auditory function was determined by recording the thresholds for the "least visible" cortical response at a series of points on the auditory cortex to the onset of pure tone stimuli. A quantitative histological study was made of the pathological changes in the organ of Corti and spiral ganglion by the technique of graphic reconstruction. Findings support previous concepts of an orderly frequency distribution within the cochlea, high frequencies at the basal end and low frequencies at the apex. Whereas, in all previous experiments we found outer hair cells to be the more susceptible to mechanical and thermal injury, there were

*From Edsel B. Ford Institute for Medical Research.

two animals in this experiment with a selecitve loss of inner hair cells. It was surprising to us to find the existence of threshold losses in these animals, an observation contradictory to the popular concept that outer hair cells normally are more easily excited than inner hair cells. The findings of this experiment correlate closely with those of the previous studies in which we observed the effect of cochlear lesions on the auditory thresholds as determined by the conditioned response method. In this respect the cortical test appears to be a reliable physiological indicator of auditory function.

DIAGNOSIS OF BILIARY TRACT DISEASE: THE PRESENT STATUE OF LIVER FUNCTION TESTS, LIVER BIOPSY AND DUODENO-BILIARY DRAINAGE. J. G. Mateer, J. I. Baltz, R. J. Priest and W. Fischbein. M. Clin. North America 40:437, 1956.

An important goal of biliary tract diagnosis is to arrive at an *early* preclinical diagnosis by conducting certain, sensitive, liver function screening tests and then to institute early therapy, including the removal of etiological factors. The popularity of annual health checks with the public offers a splendid opportunity to study patients before symptoms develop. The value of a therapeutic test in the interpretation of impaired liver function is discussed. The sensitivity, reliability and relative independent effectiveness of the liver function tests in common use are discussed, and those tests indicated for the evaluation of various types of clinical problems are outlined. The limitations of liver function tests are also enumerated. Pitfalls in the differential diagnosis of hepatic and obstructive jaundice are discussed. The value and validity of liver biopsy findings are stressed, and the remote risk and the precautions indicated in conducting this procedure are reviewed. The several indications for performing liver biopsy are enumerated, and the relation of liver biopsy to liver function tests is noted. Diagnostic duodeno-biliary drainage is evaluated and the specific indications for its use are outlined. The incidence and significance of positive microscopic findings are discussed, and the relationship of these findings to cholecystography in the diagnosis of gallstones is appraised. The importance of trained personnel is emphasized.

*HUMIDITY AND TEMPERATURE CONTROL UNIT FOR A COUNTING ROOM. L. E. Preuss. Nucleonics 14:98, April 1956.

The problem of varying temperature, high humidity and related spurious counting is outlined for the small radioisotope assay area. The inadequacy of the conventional window air conditioner is described and alterations necessary for good temperature and humidity control are detailed for a one ton, two compressor air conditioning unit. Wide range and close control are effected by means of thermostat, humidity sensing device, switching relays, two remote control temperature sensing bulbs and strip heaters.

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ORAL PHENOXYMETHYL PENICILLEN (PENICILLEN V) IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS. E. L. QUINN, J. M. COLVILLE, F. COX AND J. TRUANT. Antibiotics Annual 1955-56, pp. 502-504.

An abstract from the J. A. M. A. 160:931, 1956 embodying substantially this same material was published in the *Bulletin* 4:122, 1956.

PERSISTENT TRISMUS CAUSED BY A FOREIGN BODY: Report of Two Cases. M. REVZIN AND F. MONACO. J. Oral Surg. 14:243, 1956.

Lack of adequate mandibular excursion may be due to foreign bodies which are accidentally introduced into the temporomandibular joint region. Two cases are presented in which the foreign bodies proved to be knife blades. In each case the patient was given emergency treatment in a hospital and in each case the patient's symptoms were delayed, in one case for seven years and in the other case for eight weeks. Treatment, based on roentgenographic findings, consisted of surgical removal of the knives. In the first case, an unusually long period of time had elapsed before the foreign object was removed. In the second case, a speech resembling cleft palate speech resulted from the mechanical resistance to oronasal and oropharyngeal closure. The inability of the patient to open her mouth was also caused by a mechanical obstruction because the knife blade was lodged in the mandibular notch thereby acting as a wedge which interfered with the downward and forward excursion of the mandible.

PULMONARY ARTERIOVENOUS ANEURYSM: A Report Of Six Cases. R. J. SCHLOSSER AND H. N. HARKINS. Am. J. Surg. 91:872, 1956.

The diagnosis and management of pulmonary arteriovenous aneurysm are dealt with briefly. Six cases are presented, three patients with the diagnosis established by surgery and three patients with the diagnosis strongly supported by x-ray appearance of the lesion.

DEAFNESS AND VERTIGO FROM HEAD INJURY. H. F. SCHUKNECHT AND R. C. DAVISON. A. M. A. Arch. Otolaryngol. 63:513, 1956.

Deafness and vertigo are common following head injury. Partial permanent deafness occurs in about 50% of patients who incur a blow to the head severe enough to produce unconsciousness. Even a mild head blow, without loss of consciousness, can occasionally result in deafness. A patient sustaining a high frequency hearing loss may be unaware of the loss particularly when it involves only one ear. In such cases only audiometric testing will reveal the loss. Deafness from blows to the head may be classified into three groups: (A) Longitudinal fracture of the temporal bone, characterized by rupture of the tympanic membrane, bleeding from the ear, and an associated deafness which may be either purely conductive or the combined perceptive-conductive type. (B) Transverse fracture of the temporal bone, in which case the fracture extends through the labyrinth, thereby creating a profound loss of both auditory and vestibular function. (C) Labyrinthine concussion, in which a perceptive type of deafness results with no clinical or roentgenological evidence of temporal bone fracture. To determine the pathology responsible for the perceptive deafness and

vertigo an experiment was performed in which head blows were delivered to ten conditioned cats. Hearing tests and histological studies were made of the brains and inner ears. The hearing losses were identical with those occurring in human patients, their characteristic feature being a maximum loss at the 4000 cps frequency. Histological examination revealed damage to the organ of Corti, most severe in the upper basal turn. These changes were identical with those produced experimentally by air-borne blast and noises of high intensity. The characteristic dizziness following a head blow is of postural type and may persist for several months following head blow. It may occur independently of deafness. The underlying pathological change responsible for the postural vertigo is thought to be injury to the utricle or saccule. These structures which are sensitive to linear acceleration and deceleration are injured by the intense stimulation of the head blow. One experimental animal incurred a rupture of the membranous walls of the utricle and saccule and degenerative changes in the macula of the saccule. We believe, therefore, that deafness and vertigo following head blows are due, for the most part, to injury of the membranous labyrinth.

*ELECTRON MICROSCOPY OF A CYSTINE UROLITH. J. H. L. WATSON, J. Urol. 75:940, 1956.

The paper contains the first published electron micrographs of replicas of urolith structures. Kidney stones are difficult to replicate because they are often soft or porous, or are so insoluble in usual solvents that ordinary replicating methods are impossible. The carbon replica technique was used successfully to replicate the cystine urolith. The preparation of the replicas and some of the criteria for interpreting the micrographs are described. Electron micrographs are shown of the cystine tablets parallel and perpendicular to the (0001) planes and at intermediate angles. The compact layered nature of the stone is clearly seen. It is concluded that the carbon replica method can be used productively in the study of uroliths. It is shown that, where a cystine stone is opaque to X-rays and hard, these properties are due to efficient packing of cystine tablets into the macroscopic stone. The structure was uniform and no unique core structure was observed. There was no visible evidence of colloid, the stone apparently being a result of crystal formation from solution. In stones of other genesis it might be that colloidal structures, unique core formations, and structure in layered areas would be observable.

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